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Chemical & Pharmaceutical Bulletin, vol 32, no 12, 1984 pages 4907-4913, Tokyo, JP. I. Hayakawa et al. "Synthesis and antibacterial activities of substituted 7-oxo-2, 3-dihydro-7H-pyriod (1,2,3-de) 1,4 benzoxazine-6-carboxylic acids"

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Chemical Abstracts, vol. 104, 14th April 1986, page 382, abstract no. 126370e, Columbus Ohio USA. I.Hayakawa et al. "Synthesis and antibactrial activities of optically-active ofloxacin" & Antimicrob. Agents Chemother., 1986, 29(1), 163-4

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Description

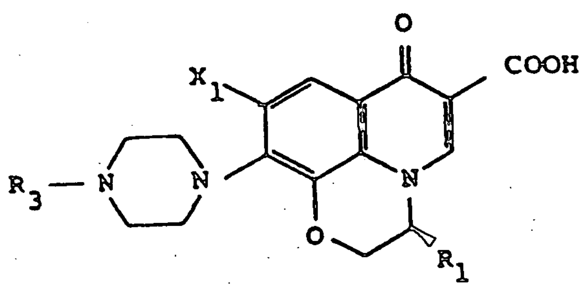
Ofloxacin ((±)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]-benzoxazine-6-carboxylic acid) is known to be an excellent synthetic antimicrobial agent as disclosed in European Patent Specification EP-B-47 005.

Ofloxacin has an asymmetric carbon atom at the 3-position thereof and is obtained as a racemate (specific rotation $[\alpha]_D = 0°$) by known processes. The present inventors obtained optically active compounds of the racemic Ofloxacin and found that the S(-)-compound of ofloxacin possesses an antimicrobial activity of about 2 times higher than that of the (±)-compound and an acute toxicity (LD_{50}) weaker than that of the (±)-compound as determined in mice by intravenous administration. On the other hand, the present inventors found that the R(+)-compound exhibits an antimicrobial activity of only about 1/10 to 1/100 times that of the (±)-compound, whereas it possesses an acute toxicity substantially equal to that of the (±)-compound. That is, the S(-)-form of Ofloxacin has been found to have very desirable properties, i.e., increased antimicrobial activity and reduced toxicity, and is expected to be a very useful pharmaceutical agent as compared with the (±)-compound. Further, both the R(+)- and S(-)-compounds of Ofloxacin in the free form have markedly increased water-solubility as compared with (±)-compound and as compared with free compounds of this type, and can be used in injectable preparations. These advantages will be apparent from the experimental data shown hereinafter.

An object of this invention is to provide an optically active isomer of Ofloxacin and its analogs.

Another object of this invention is to provide a novel process for preparing an optically active isomer of Ofloxacin and its analogs.

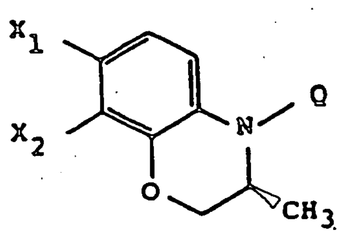
The present invention relates to an optically active isomer of Ofloxacin and its analogs which can be represented by the formula (VI):



(VI)

wherein X_1 represents a fluorine atom, R_1 represents a methyl group, and R_3 represents a methyl or an ethyl group.

The optically active isomer of Ofloxacin and its analogs of the invention can be prepared by any of Processes A, B and C shown below. Important intermediates are the compounds of formula X:

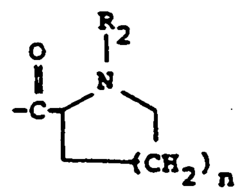


(X).

wherein X_1 is a fluorine atom and X_2 is a halogen atom, such as a fluorine atom or a chlorine atom, and preferably both X_1 and X_2 are fluorine atoms;

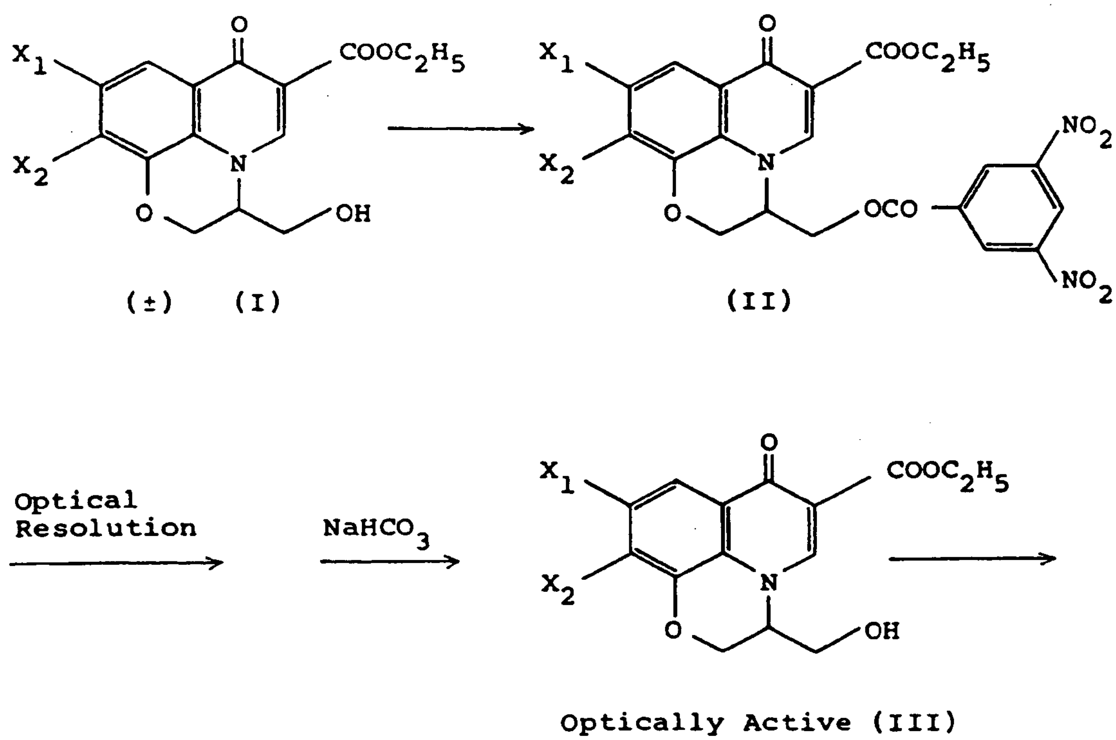
Q represents

a hydrogen atom or a group

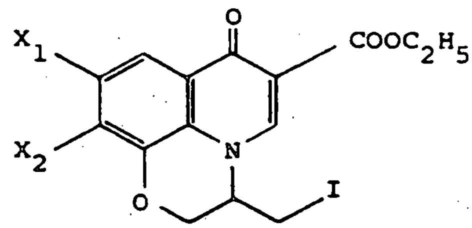


wherein R_2 represents a substituted sulfonyl group, an alkoxycarbonyl group or an aralkyloxycarbonyl group, such as a p-toluenesulfonyl group, a benzenesulfonyl group, a methanesulfonyl group, a t-butoxycarbonyl group, a benzyloxycarbonyl group, a p-methoxybenzyloxycarbonyl group, etc., preferably a substituted sulfonyl group, and more preferably a p-toluenesulfonyl group: and n represents an integer of from 1 to 3 and preferably 1 or 2.

Process A:

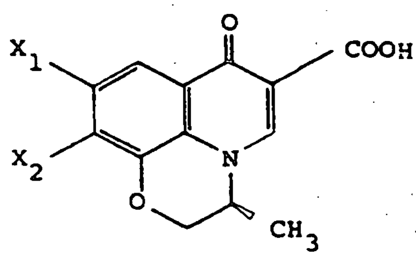


$\xrightarrow[\text{DMF}]{(PhO)_3P^+CH_3\ I^-}$

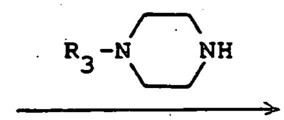


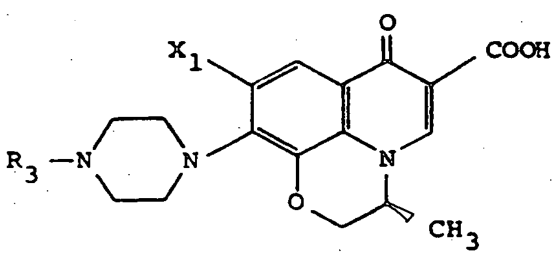
(IV)

$\xrightarrow[\text{2) AcOH - HCl}]{\text{1) } nBu_3SnH/EtOH}$



(V')





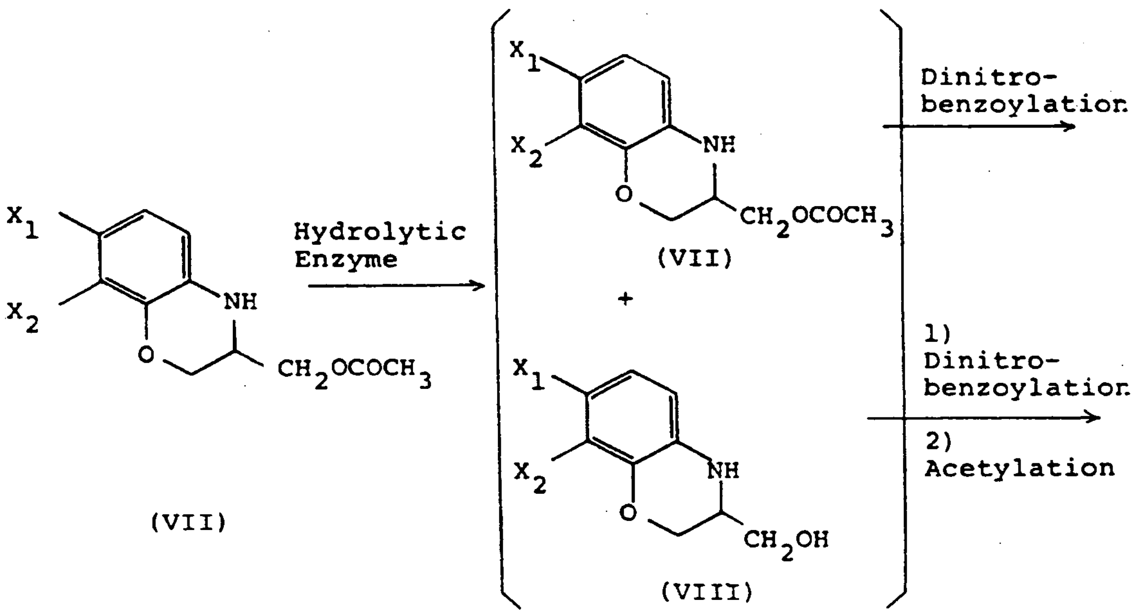
(VI')

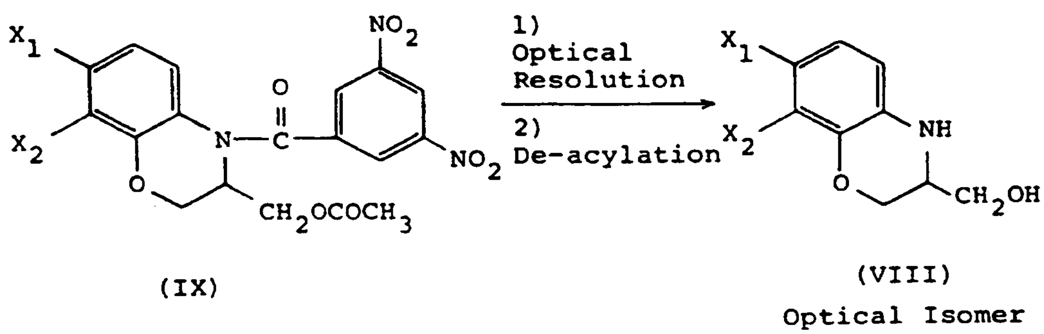
wherein X_1, X_2 and R_3 are as defined above.

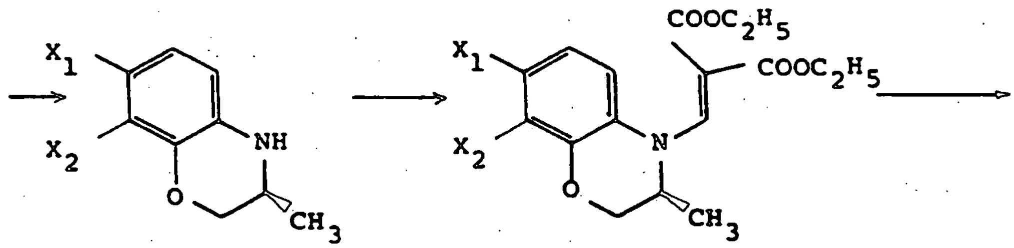
More specifically, the (±)-3-hydroxymethyl compound (I) is treated with 3,5-dinitrobenzoyl chloride, etc. to obtain its derivative, such as the (±)-3,5-dinitrobenzoate compound (II), which is then optically resolved into two optically active compounds by an appropriate method, such as high performance liquid chromatography (HPLC). The subsequent procedures can be applied to either of the S(-)-compound and the R(+)-compound to lead to the respective final product, but in view of the purpose of the present invention, the final product (VI') is shown as S(-)-form.

The resulting optically active compound is treated with sodium hydrogencarbonate, etc. to selectively hydrolyze the benzoate moiety to form the hydroxymethyl compound (III). The hydroxymethyl compound is converted into the 3-iodomethyl compound (IV) by using an iodinating reagent, which is then reduced with n-tributyltin hydride, etc. to prepare the 3-methyl compound. This compound, without being isolated and purified, can be hydrolyzed as such under an acidic condition to obtain the 3-methyl-6-carboxylic acid (V'). The carboxylic acid is then reacted with N-methyl or N-ethylpiperazine by, for example, heating while stirring to obtain the 10-(4-methyl or ethylpiperazinyl) compound (VI') as a final product.

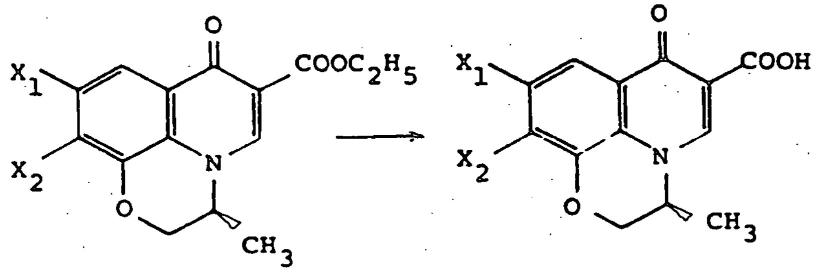
Process B:


X_1
X_2
NH
O
CH_2OCOCH_3
(VII)
Hydrolytic Enzyme
X_1
X_2
NH
O
CH_2OCOCH_3
(VII)
+
X_1
X_2
NH
O
CH_2OH
(VIII)
Dinitro-benzoylation
1) Dinitro-benzoylation
2) Acetylation

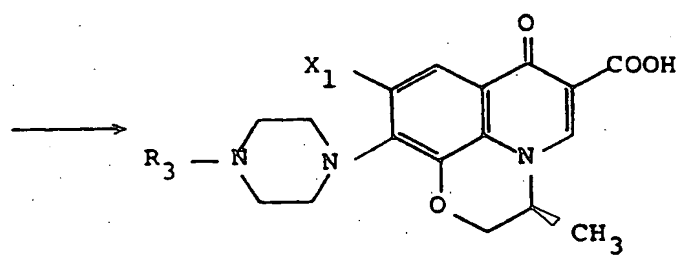

X_1
X_2
N
O
C
O
NO_2
NO_2
CH_2OCOCH_3
(IX)
1) Optical Resolution
2) De-acylation
X_1
X_2
NH
O
CH_2OH
(VIII)
Optical Isomer



(X')   (XI')



(XII')   (V')



(VI')

wherein X_1, X_2 and R_3 are as defined above.

As described previously, 7,8-difluoro-2,3-dihydro-3-methyl-4H-[1,4]benzoxazine having the formula (X) wherein X_1 and X_2 represent fluorine atoms and Q represents a hydrogen atom is an important intermediate for synthesizing Ofloxacin. The inventors have conducted various investigations on an advantageous process for preparing an optical isomer of this compound expecting that such would be a useful starting material for synthesizing the S(-)-isomer of Ofloxacin.

As a result, it has been found that when racemic 7-fluoro-8-halogeno-2,3-dihydro-3-acetoxymethyl-4H-[1,4]benzoxazine (VII), as a substrate, is hydrolyzed with an appropriate enzyme, such as a certain kind of lipase, to form a 7-fluoro-8-halogeno-2,3-dihydro-3-hydroxymethyl-4H-[1,4]benzoxazine (VIII), there is a difference in the rate of hydrolysis between the (+)-isomer and the (-)-isomer.

For example, the compound (VII) was reacted with lipoprotein lipase (LPL Amano 3 derived from Pseudomonas aeruginosa, produced by Amano Seiyaku K.K.) or lipase (derived from Porcine pancreas, produced by Shigma Chemical Company (U.S.A.); derived from Candida cylindracea, produced by Shigma

Chemical Company; or derived from Rhizopus delemar, produced by Seikagaku Kogyo Co., Ltd.), and the reaction with time was determined through HPLC (column: TSK gel ODS-120A, 4.6 x 250 mm; solvent: acetonitrile/water = 1/1 by volume; velocity: 1 ml/min). When the rate of hydrolysis reached about 55%, the compound (VII) was recovered and led to the 3,5-dinitrobenzoyl derivative (IX). The resulting reaction product was quantitatively determined by HPLC (column: Sumipacks OA-4200, 4.0 x 250 mm; solvent: n-hexane/1,2-dichloroethane/ethanol = 92/6.4/1.6 by volume; velocity: 1.6 ml/min) to obtain the ratio of the (+)-isomer/(-)-isomer of the compound (VII). The results obtained are shown in Table 1 below.

Table 1

Enzyme (Origin)	Rate of Hydrolysis (%)	(+)/(-)
LPL Amano 3 (P. aeruginosa)	54.7	23.0/77.0
Lipase (R. delemar)	53.6	42.6/57.4
Lipase (C. cylindracea)	54.5	61.9/38.1
Lipase (P. pancreas)	55.2	56.8/43.2

These results lead to the conclusion that the optically active compounds (VII) and (VIII) can be obtained by utilizing the so-called asymmetric hydrolysis with these enzymes.

Process B according to the present invention comprises reacting a racemic 7-flouro-8-halogeno-2,3-dihydro-3-acetoxymethyl-4H-[1,4]benzoxazine (VII) with an asymmetric hydrolytic enzyme to recover a mixture comprising the starting compound (VII) rich in either one of optical isomers and a 3-hydroxymethyl compound (VIII), separating the mixture into each compound, dinitrobenzoylating either one or both of these compounds and further acetylating the benzoylated 3-hydroxymethyl compound (VIII) to obtain the compound (IX), separating the compound into the optical isomers by crystallization, subjecting the resulting desired optical isomer to deacylation and dehydroxylation by means of known chemical processes to obtain an optically active 7-flouro-8-halogeno-2,3-dihydro-3-methyl-4H-[1,4]benzoxazine (X') and then obtaining therefrom optically active Ofloxacin or its analog (VI') by known processes.

Process B of the invention will further be illustrated in some detail referring to specific examples.

The racemic compound (VII) is dissolved in a 0.1M phosphoric acid buffer (pH 7.0), and lipoprotein lipase (LPL Amano 3) is added to the solution to cause enzymatic reaction at 37°C. By this reaction, the (+)-compound is preferentially hydrolyzed to thereby form a mixture of the compound (VII) rich in the (-)-isomer and the compound (VIII) rich in the (+)-isomer. The reaction mixture is recovered in an appropriate stage by extraction with an organic solvent, such as ethyl acetate.

The above enzymatic reaction may also be carried out in an appropriate organic solvent, such as a mixed solvent of benzene and n-hexane, by using a hydrophilic resin, e.g., DEAE-Toyopearl 650M or Toyopearl HW-40, etc., or Celite as a dispersing agent or by using a resin, such as Amberlite XAD-7, Butyl-Toyopearl 650M, etc., as an adsorptive fixing agent. In addition, use of inclusive fixing agents, such as photo-crosslinked resins, urethane prepolymers, etc., is also considered to make it possible to effect the enzymatic reaction in an organic solvent.

The reaction in an organic solvent with an aid of appropriate dispersing agents or fixing agents as described above is advantageous in that the substrate can be reacted at higher concentrations than in an aqueous solution and that post-treatments after the reaction can be simplified. Actually, in the case of performing the reaction in an organic solvent, the reaction mixture can be recovered in high yields simply by filtering the dispersing agent or fixing agent in an appropriate stage and concentrating the filtrate. Moreover, the fixing agents can be repeatedly reused to advantage.

The compounds (VII) and (VIII) in the reaction mixture can be separated and purified by a usual method of separation, such as silica gel column chromatography. The thus separated compound (VII) is treated, for example, with 3,5-dinitrobenzoyl chloride in tetrahydrofuran in the presence of pyridine to form the 3,5-dinitrobenzoyl derivative (IX), which is then recrystallized from an appropriate solvent, e.g., a mixed solvent of ethyl acetate and n-hexane, whereby the racemate is preferentially crystallized. The racemic crystals are separated by filtration, and the (-)-7-flouro-8-halogeno-2,3-dihydro-3-acetoxymethyl-4H-[1,4]benzoxazine 3,5-dinitrobenzoyl derivative (IX) having a high optical purity is obtained from the filtrate.

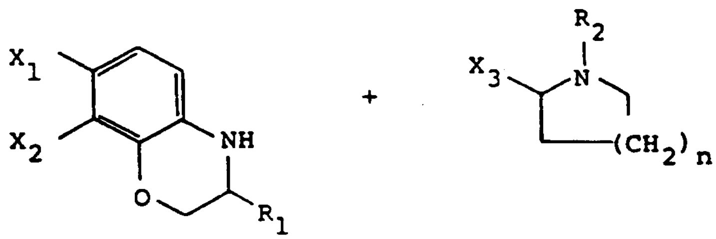
The compound (IX) is then subjected to de-acylation treatment by, for example, hydrolysis under an alkaline condition to form the (-)-isomer of the compound (VIII). This compound is dissolved in pyridine and treated with thionyl chloride, and the product is further subjected to dehydroxylation in a usual manner, such as reduction with sodium borohydride in dimethyl sulfoxide, to thereby obtain the (-)-7-flouro-8-halogeno-2,3-dihydro-3-methyl-4H-[1,4]benzoxazine (X') having an optical purity of 99% or higher.

When the racemic compound (VII) is treated with lipase (derived from Candida cylindracea or Porcine Pancreas), the (-)-compound is preferentially hydrolyzed to obtain the compound (VIII) rich in the (-)-isomer. The resulting compound is led to a compound in the form of the compound (IX), which is then treated in accordance with the procedures as described above, such as separation by crystallization, to form the (-)-isomer of the compound (VIII). The (-)-isomer of the compound (X') can then be prepared from this product in the same manner as described above with a high purity.

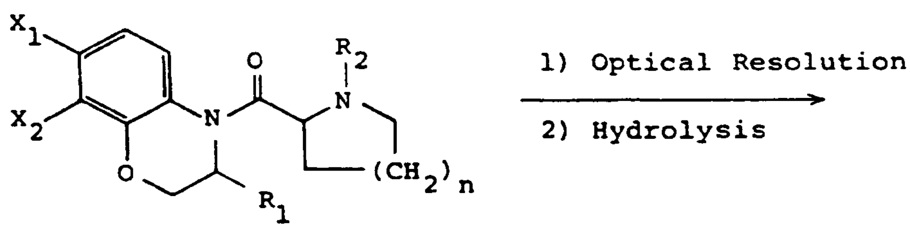
Other asymmetric hydrolyses which can achieve the object of the present invention in addition to the above-recited enzymes can be found based on the above-mentioned elucidation. Further, when it is intended to obtain (+)-compounds, the same procedures as described above can be followed based on the above elucidation.

The (-)-compound of Ofloxacin and analogs thereof can be prepared from the novel intermediates of the present invention having the formula (X') in accordance with Process C as illustrated below.

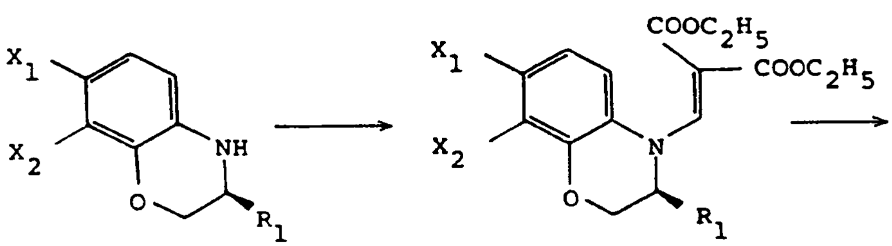
Process C:



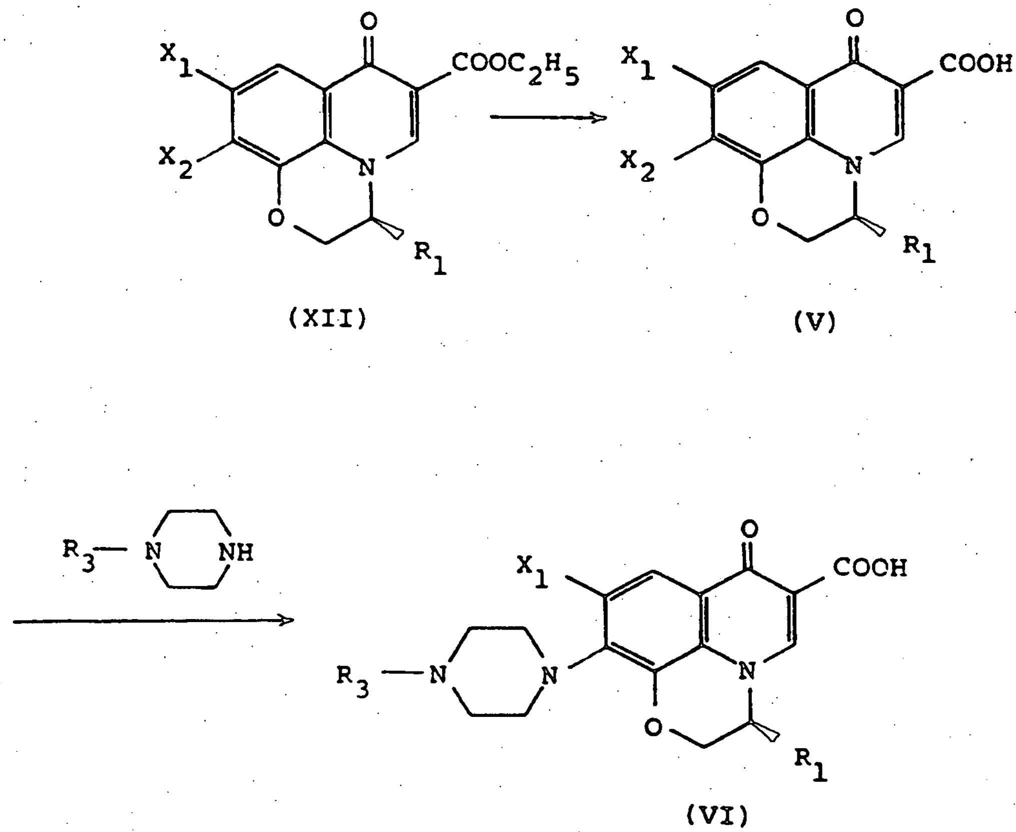
(X')　　　　(XIV)



(X")



(X)　　　　(XI)



wherein n, X_1, X_2, R_2 and R_3 are as defined above, R_1 is methyl and X_3 is a carboxyl group or a reactive derivative thereof, for example, an active ester, a halide or an acid anhydride of the carboxylic acid.

In Process C, the 7-flouro-8-halogeno-1,4-benzoxazine derivative (X') is condensed with a cyclic amino acid or a reactive derivative thereof (XIV) through amide linkage formation to produce the compound (X"). The condensation reaction can be effected by either one of the active ester method, the acid anhydride method or the DCC method, but, generally, the compound (X') and an acid chloride (XIV) wherein X_3 is -COCl are reacted in an organic solvent such as halogenated hydrocarbons. e.g., dichloromethane, in the presence of an acid acceptor such as pyridine, triethylamine or potassium carbonate, at room temperature while stirring. The reaction product can be isolated and purified in a conventional manner, such as crystallization, column chromatography, etc.

In this condensation reaction, when either one of the two isomers of the cyclic amino acid or its reactive derivative (XIV), i.e., an S-compound or an R-compound, is used, separation of the diastereomeric mixture of the compound (X") can be carried out easily. More specifically, derivatives (XIV), such as S- or R-proline, S- or R-pipecolic acid (piperidine-2-carboxylic acid), etc., are suitably used. The most preferred compounds (XIV) include (S)-N-benzenesulfonylproline and (S)-N-p-toluenesulfonylproline.

The diastereomeric mixture of the compound (X") can be separated by fractional crystallization, chromatography using silica gel, etc. as a carrier, or a combination thereof.

The thus separated diastereomer is hydrolyzed, usually under a basic condition, to form a 7-flouro-8-halogeno-3-(S)-methyl-[1,4]benzoxazine (X). This compound can be led to the 9-flouro-10-halogeno-3-(S)-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid (V) through known reactions, which can then be converted to the 10-(4-methyl or ethylpiperazinyl) compound (VI).

Of the above-described Processes A, B and C, the particularly preferred is Process C.

Antimicrobial Activity

The antimicrobial activities of the optical isomers [(-) and (+)] of Ofloxacin and an analog compound to various microorganisms were compared with that of Ofloxacin (racemate), and the results are shown in

Table 2 below. The test method was in accordance with the standard method specified by The Japan Society of Chemotherapy.

Table 2

Minimum Inhibitory Concentration (MIC; μg/ml)

Microorganism	S(-)- Ofloxacin *	Racemic Ofloxacin	R(+)- Ofloxacin	Compound of Example 17
E. coli, NIHJ	<0.1	<0.10	0.39	<0.1
K. pneumoniae, Type 2	<0.1	0.10	1.56	<0.1
Ser. marcescens, 10100	<0.1	0.10	1.56	<0.1
Ps. aeruginosa, 32104	0.39	0.78	12.5	0.39
Ps. aeruginosa, 32121	0.10	0.20	6.25	0.10
Ps. maltophilia, IID1275	0.39	0.78	12.5	0.10
S. aureaus, Smith	0.10	0.20	6.25	<0.1
S. aureaus, 209P	0.20	0.39	25	0.10
Str. pyogenes, G-36	0.78	1.56	<100	1.56

Acute Toxicity

The acute intravenous toxicity of (±), R(+) and S(-)-forms of Ofloxacin in male mice is shown in Table 3 below.

Table 3

Compounds	Dose (mg/kg)	Numbers of mice	Day after treatment			Mortality
			1	2	3	
(±)	100	5	0	0	0	0/5
	200	5	2	0	0	2/5
	400	5	5	0	0	5/5
R(+)	100	5	0	0	0	0/5
	200	5	3	0	0	3/5
	400	5	5	0	0	5/5
S(-)	100	5	0	0	0	0/5
	200	5	0	0	0	0/5
	400	5	5	0	0	5/5
LD_{50} (i.v. in mice) (±)-form 203 mg/kg S(-)-form 244 mg/kg						

Solubility

The solubility of (±), R(+) and S(-)-forms of Ofloxacin in water at a temperature in the range of from 23° to 26°C is shown in Table 4 below.

Table 4

Compounds	Water-Solubility (μg/ml)
(±)	2,400
R(+)	25,800
S(-)	22,500

The conversion of the intermediates of the formula (X) into the desired Ofloxacin or an analog thereof can be carried out by a well known process as disclosed, for example, in U.S. Patent 4,382,892, European Patent Specification EP-B-47005, Japanese Patent Application (OPI) Nos. 29789/83 and 43977/83.

This invention will now be illustrated in greater detail with reference to the following examples, but it should be understood that they are not intended to limit the present invention. Examples 1 to 7 describe preparation of Ofloxacin according to Process A; Examples 8 to 11 describe preparation of Ofloxacin according to Process B; and Examples 12 to 17 describe preparation of Ofloxacin and analog compounds according to Process C.

EXAMPLE 1

Preparation of Benzoyloxy Compound

One gram of (±)-9,10-difluoro-3-hydroxymethyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid ethyl ester (I) and 500 mg of pyridine were suspended in 100 ml of anhydrous tetrahydrofuran (THF), and 1.6 g of 3,5-dinitrobenzoyl chloride was added thereto, followed by refluxing at 90°C. The suspension was once dissolved, and a colorless precipitate was then formed. The reaction was continued for 1.5 hours. After cooling, the precipitate was collected by filtration, washed with methanol and diethyl ether and dried to obtain 1.2 g of (±)-9,10-difluoro-3-(3,5-dinitrobenzoyloxy)methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid ethyl ester (II) as a colorless powder having a melting point of 240-242°C.
NMR ($CDCl_3$/5% DMSO-d_6) δ(ppm);

1,30 (3H, t, J=7.0Hz, $-CH_2CH_3$), 4.26 (2H, q, J=7.0Hz, $-CH_2CH_3$), 4.4 - 4.5 (5H, m), 7.76 (1H, dd, J=11.0Hz, 7.0Hz, C_8-H), 8.8 (1H, s, C_5-H), 9.0 (2H, d, J=3.0Hz, aromatic ring proton) and 9.2 (1H, t, J=3.0Hz, aromatic ring proton)

EXAMPLE 2

Optical Resolution

Six milligrams of the benzoyloxy compound as obtained in Example 1 was dissolved in about 0.6 ml of dimethylformamide (DMF) which had been purified by distillation. The solution was filtered through a millipore filter and subjected to HPLC using a column of Sumipacks OA-4200 (2 cm x 25 cm) and a solvent of n-hexane/1,2-dichloroethane/ethanol = 6/3/1 (by volume) at a velocity of 8 ml/min.

Since the initial fractions (fractions of the (+)-compound) contained a slight amount of the racemic compound (I) due to partial hydrolysis when dissolved in DMF, they were further purified by silica gel chromatography using chloroform to 10% methanol/chloroform as an eluent. These purification procedures were repeated to thereby obtain 250 mg each of the two optically active compounds [(-)-isomer and (+)-isomer] from 600 mg of the benzoyloxy compound (II).

(+)-Isomer: retention time: 56 - 76 mins. (column temperature: 22°C); melting points: 235 - 240°C; $[\alpha]_D^{23}$ = +90.8° (c = 0.852, DMF)

(-)-Isomer: retention time: 78 - 98 mins. (column temperature: 22°C); melting points: 244 - 249°C; $[\alpha]_D^{23}$ = -92.5° (c = 0.889, DMF)

EXAMPLE 3

Preparation of Ethyl (-)-9,10-Difluoro-3-Hydroxymethyl-7-Oxo-2,3-Dihydro-7H-Pyrido[1,2,3-de][1,4]-Benzoxazine-6-Carboxylate (III)

In a mixture of 10 ml of ethanol and 4 ml of a saturated aqueous solution of sodium bicarbonate, 120 mg of the optically active benzoyloxy compound [(-)-isomer] were suspended, and the suspension was heated at 50 to 60°C for 2 hours while stirring. After concentration, water was added to the reaction mixture, and any insoluble material was collected by filtration, washed successively with water, 95% ethanol and diethyl ether to obtain 68 mg of the optically active 3-hydroxymethyl compound [(III), (-)-isomer) as colorless crystals having a melting point of 235 - 240°C.

Elementary Analysis for $C_{15}H_{13}F_2NO_5$:			
Calcd. (%):	C 55.39,	H 4.03,	N 4.31
Found (%):	C 55.44,	H 4.01,	N 4.49

$[\alpha]_D^{23}$ = -125.9° (c = 0.918, DMF)

In the same manner as described above, the (+)-3-hydroxymethyl compound was synthesized from the (+)-benzoyloxy compound. Melting point: 231 - 234°C. $[\alpha]_D^{23}$ = +125.9° (c = 0.715, DMF).

EXAMPLE 4

Preparation of Ethyl (-)-9,10-Difluoro-3-Iodomethyl-7-oxo-2,3-Dihydro-7H-Pyrido-[1,2,3-de][1,4]Benzoxazine-6-Carboxylate (IV)

In 12 ml of anhydrous DMF were suspended 63 mg of the (-)-3-hydroxymethyl compound (III), and the suspension was heated at 70 to 80°C with stirring to form a solution, followed by allowing to cool to room temperature. To the solution were added 340 mg of triphenylphosphite methiodide, followed by stirring for 1.5 hours. The solvent was removed by distillation under reduced pressure, and the residue was dissolved in chloroform. The solution was partitioned with a sodium thiosulfate aqueous solution and then with a saturated sodium chloride aqueous solution. The chloroform layer was dried over anhydrous magnesium sulfate, and the solvent was removed by distillation. To the residue was added diethyl ether, followed by stirring, and the precipitated solid was collected by filtration, washed with diethyl ether and dried under reduced pressure to obtain 78 mg of the corresponding iodomethyl compound (IV) as a white powder having a melting point of 214 - 217°C.

Elementary Analysis for $C_{15}H_{12}F_2INO_4$:			
Calcd. (%):	C 41.40,	H 2.78,	N 3.22
Found (%):	C 41.16,	H 2.58,	N 2.99

The (+)-compound was obtained in the same manner as described above.

EXAMPLE 5

Preparation of S(-)-9,10-Difluoro-3-Methyl-7-Oxo-2,3-Dihydro-7H-Pyrido-[1,2,3-de][1,4]Benzoxazine-6-Carboxylic Acid (V')

In 18 ml of absolute ethanol was suspended 78 mg of the iodomethyl compound (IV), and the suspension was heated at 60 to 70 °C with stirring to form a solution, followed by allowing to cool to room temperature. To the resulting solution was added 0.2 ml of n-tributyltin hydride, and the mixture was stirred at 50 to 60 °C for 1 hour and then at room temperature for 1 hour. The solvent was removed by distillation, and the residue was subjected to column chromatography using 8 g of silica gel as a carrier and chloroform:methanol (40:1 by volume) as an eluent to obtain a crude methyl compound. The crude product was dissolved in 2 ml of glacial acetic acid, and 4 ml of concentrated hydrochloric acid was added thereto. After heating at reflux for 40 minutes, the reaction mixture was concentrated. Water was added to the concentrate, and the thus precipitated crystal was collected by filtration, washed successively with water, ethanol and diethyl ether and dried under reduced pressure to obtain 22 mg of crystals of the S(-)-compound (V') having a melting point of 300 °C or higher.

Elementary Analysis for $C_{13}H_9F_2NO_4$:			
Calcd. (%):	C 55.52,	H 3.23,	N 4.98
Found (%):	C 55.79,	H 3.20,	N 4.91

$[\alpha]_D^{23}$ = -65.6° (c = 0.950, DMSO)

EXAMPLE 6

Preparation of S(-)-9-Fluoro-3-Methyl-10-(4-Methyl-1-Piperazinyl)-7-Oxo-2,3-Dihydro-7H-Pyrido[1,2,3-de]-[1,4]Benzoxazine-6-Carboxylic Acid

In 3 ml of anhydrous dimethyl sulfoxide were dissolved 21 mg of the S(-)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid (V') and 30 mg of N-methylpiperazine, and the solution was stirred at 130 to 140 °C for 1 hour. The solvent was removed by distillation, and to the residue was added 2 ml of ethanol. The thus precipitated solid was collected by filtration and washed successively with a small amount of ethanol and diethyl ether. The resulting powder weighing 14 mg was passed through a column of 5 g of silica gel and eluted with a lower layer solution of chloroform-methanol-water (7:3:1 by volume) to obtain the title compound, S(-)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid (VI'). The mother liquor left after the filtration was subjected to thin layer chromatography (silica gel; 20 cm x 20 cm, 5 mm (t)) and developed with a lower layer solution of chloroform-methanol-water (15:3:1 by volume). Both the purified products were combined to yield 14 mg of the title compound as crystals having a melting point of 220 - 228 °C (with decomposition).

Elementary Analysis for $C_{18}H_{20}FN_3O_4$:			
Calcd. (%):	C 59.82,	H 5.58,	N 11.63
Found (%):	C 60.01,	H 5.69,	N 11.53

$[\alpha]_D^{24}$ = -68.8° (c = 0.711, 0.05N NaOH)
MS (m/e): 361 (M^+)
NMR ($CDCl_3$) δ(ppm):

1.63 (3H, d, C_3-CH_3), 2.38 (3H, s, N-CH_3), 2.54 - 2.60 (4H, m, 2 x CH_2N), 3.40 - 3.44 (4H, m, 2 x CH_2N), 4.35-4.52 (3H, m, CH and CH_2), 7.76 (1H, d, aromatic ring C_8-H) and 8.64 (1H, s, C_5-H)

The (+)-compound was obtained in the same manner as described above. Melting point: 218 - 226°C (with decomposition). $[\alpha]_D^{24}$ = +68.7° (c = 0.560, 0.05N NaOH). MS (m/e): 361 (M^+).

EXAMPLE 7

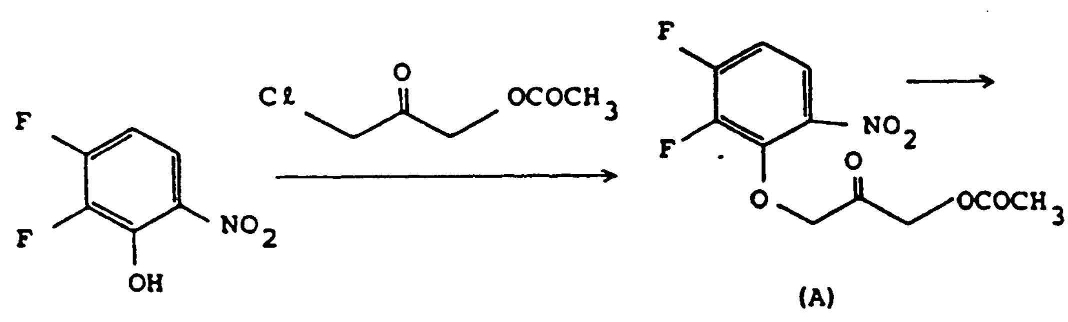
Preparation of S(-)-9-Fluoro-3-Methyl-10-(4-Methyl-1-Piperazinyl)-7-Oxo-2,3-Dihydro-7H-Pyrido[1,2,3-de]-[1,4]Benzoxazine-6-Carboxylic Acid (VI')

In 30 ml of diethyl ether were suspended 281 mg of the S(-)-9,10-diflouro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]-benzoxazine-6-carboxylic acid (V') as obtained in Example 5, and a large excess of boron trifluoride ethyl etherate was added thereto while stirring at room temperature, followed by allowing the mixture to react for 45 minutes. The precipitate formed was collected by filtration, washed with diethyl ether and dried under reduced pressure. The resulting chelate compound weighing 310 mg was dissolved in 6 ml of dimethyl sulfoxide, and 0.32 ml of triethylamine and 0.13 ml of N-methylpiperazine were added to the solution. The mixture was stirred at room temperature for 17 hours, followed by concentration to dryness under reduced pressure. The residue was washed with diethyl ether and then dissolved in 20 ml of 95% ethanol containing 0.5 ml of triethylamine, and the solution was heated at reflux for 8 hours. After cooling, the reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in 5% diluted hydrochloric acid, and the solution was distributed between chloroform and water. The aqueous layer was adjusted to a pH of 11 with 1N sodium hydroxide and then to a pH of 7.4 with 1N hydrochloric acid. The solution was extracted three times with 50 ml portions of chloroform, and the extract was dried over sodium sulfate. The chloroform was removed by distillation. Recrystallization of the resulting powder from ethanol-diethyl ether gave 120 mg of the title compound as transparent fine needle-like crystals having a melting point of 225 - 227°C (with decomposition). $[\alpha]_D^{24}$ = -76.9° (c = 0.385, 0.05N NaOH)

Elementary Analysis for $C_{18}H_{20}FN_3O_4.1/2H_2O$:			
Calcd. (%):	C 58.37,	H 5.72,	N 11.35
Found (%):	C 58.17,	H 5.58,	N 11.27

REFERENCE EXAMPLE 1

Preparation of (±)-3-Acetoxymethyl-7,8-Difluoro-2,3-Dihydro-4H-[1,4]Benzoxazine



In 1.0 liter of acetone were dissolved 60.0 g of 2,3-difluoro-6-nitrophenol, and 70.0 g of 1-acetoxy-3-chloro-2-propane and then 33.1 g of potassium carbonate were added to the solution while stirring at room temperature. After stirring for an additional 30 minutes, 6.6 g of potassium iodide were added thereto, and the mixture was refluxed for 4 hours. After allowing to cool, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The concentrate was dissolved in 4.0 liters of a mixed solvent of ethyl acetate:benzene (1:1 by volume). The resulting solution was washed with water, dried over anhydrous

sodium sulfate and concentrated under reduced pressure. The concentrate was subjected to column chromatography using 1.2 kg of silica gel and benzene/ethyl acetate (10/1) as an eluent to obtain 32.8 g of Compound (A) as an oily product. Compound (A) was dissolved in 300 ml of methanol, and 115 ml of Raney nickel was added thereto to effect catalytic reduction under atmospheric pressure. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography by using 400 g of silica gel and benzene/ethyl acetate (10/1 by volume) as an eluent, and the product was recrystallized from benzene-n-hexane to obtain 17.9 g of (±)-3-acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine (VII) as colorless crystals having a melting point of 73 - 74 °C.

Elementary Analysis for $C_{11}H_{11}F_2NO_3$:			
Calcd. (%):	C 54.32,	H 4.56,	N 5.76
Found (%):	C 54.09,	H 4.42,	N 5.76

EXAMPLE 8

Preparation of (-)-3-Acetoxymethyl-7,8-Difluoro-2,3-Dihydro-4H-[1,4]Benzoxazine-3,5-Dinitrobenzoyl Derivative (IX)

a) Ten grams of (±)-3-acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine (VII) as a substrate were dissolved in 1.00 liter of a mixed solvent of benzene/n-hexane (4/1 by volume). A resin in a wet state which was prepared by suspending 100 ml of DEAE-Toyopearl 650M in a 0.05M phosphoric acid buffer (pH 7.0) followed by filtration by suction and 200 mg of lipoprotein lipase (LPL Amano 3) were added to the above-prepared substrate solution. The reaction system was allowed to react at 37 °C for 6 hours under stirring. The reaction mixture was filtered by suction, and the resin was washed with 200 ml of benzene. The filtrate and the washing were combined and concentrated under reduced pressure. The concentrate weighing 9.68 g was subjected to column chromatography using 200 g of silica gel as a carrier and benzene/ethyl acetate (10/1 by volume) as an eluent to obtain 4.67 g of 3-acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine.

The resulting compound was dissolved in 200 ml of tetrahydrofuran, and 5.76 g of 3,5-dinitrobenzoyl chloride and 3.3 ml of pyridine were added thereto, followed by heating at 60 °C for 3 hours. The reaction mixture was concentrated under reduced pressure, and the concentrate was dissolved in 400 ml of ethyl acetate, washed successively with diluted hydrochloric acid, an aqueous solution of sodium bicarbonate and water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Addition of n-hexane to the concentrate caused precipitation of pale yellow crystals of a racemate. After sufficient precipitation, the precipitate was separated by filtration, and the filtrate was concentrated by dryness to obtain 3.93 g of the 3,5-dinitrobenzoyl derivative of the (-)-3-acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine (IX).

b) To about 2.0 ml of Amberlite XAD 7 were added 2.0 ml of a 0.05M phosphoric acid buffer (pH 7.0) having dissolved therein 20 mg of lipoprotein lipase (LPL Amano 3), and the system was allowed to stand at room temperature for 18 hours to thereby adsorb the enzyme onto the resin. The resin was filtered by suction and washed with 10 ml of a 0.05M phosphoric acid buffer (pH 7.0). A solution of 250 mg of (±)-3-acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine as a substrate in 25 ml of a mixed solvent of benzene and n-hexane (4:1 by volume) was added to the thus prepared resin in a wet state, followed by allowing to react at 37 °C for 4 hours under stirring. The reaction mixture was worked-up in the same manner as described in a) above to obtain 117 mg of optically active 3-acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine. In the same manner, there were obtained 65 mg of the 3,5-dinitrobenzoyl derivative of the (-)-3-acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine.

c) To 3.60 liters of a 0.1M phosphoric acid buffer (pH 7.0) were added 3.60 g of (±)-3-acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine as a substrate, and the mixture was stirred at 37 °C for 18 hours to form a solution. To the resulting solution were added 50 mg of lipoprotein lipase (LPL Amano 3), followed by allowing the system to react at 37 °C for 190 minutes while stirring. The reaction mixture was extracted three times with 2.0 liter portions of ethyl acetate. The combined extract was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The concentrate was subjected to column chromatography using 70 g of silica gel as a carrier and chloroform as an eluent to obtain 1.07 g of optically active 3-acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine. The resulting compound was treated in the same manner as described in a) above to obtain 0.9 g of the

3,5-dinitrobenzoyl derivative of the (-)-3-acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine.

d) To 3.70 liters of a 0.1M phosphoric acid buffer (pH 7.0) were added 3.70 g of (±)-3-acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine as a substrate, followed by stirring at 37°C for 3.5 hours to form a solution. To the resulting solution were added 2.22 g of lipase (derived from Candida cylindracea), followed by allowing the system to react at 37°C for 7.5 hours while stirring. The reaction mixture was extracted three times with 2.0 liter portions of ethyl acetate. The combined extract was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The concentrate was subjected to column chromatography using 70 g of silica gel and developed first with benzene/ethyl acetate (5/1 by volume) to elute 3-acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]-benzoxazine and then with benzene/ethyl acetate (1/1 by volume) to elute 7,8-difluoro-2,3-dihydro-3-hydroxymethyl-4H-[1,4]benzoxazine.

The latter eluate weighing 1.31 g was dissolved in 60 ml of tetrahydrofuran, and 1.70 g of 3,5-dinitrobenzoyl chloride was added thereto, followed by heating at 37°C for 20 hours. The reaction mixture was concentrated under reduced pressure, and the concentrate was dissolved in 400 ml of ethyl acetate, washed successively with a sodium bicarbonate aqueous solution and water, dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure to obtain 2.52 g of a reaction product. The reaction product was dissovled in 10 ml of pyridine, and 10 ml of acetic anhydride was added thereto, followed by heating at 37°C for 20 hours. The reaction mixture was worked-up and recrystallized in the same manner as described in a) above to remove the racemate crystals to thereby increase optical purity. Since the product still contained slight amounts of the reaction by-products, it was further purified by Toyopearl HW-40-column chromatography (column: 2.5 x 95 cm; developing solvent: methanol/acetonitrile = 1/1 by volume) and then silica gel column chromatography (column: 1.8 x 34 cm; developing solvent; chloroform/acetone = 20/1 by volume) to finally obtain 0.44 g of the 3,5-dinitrobenzoyl derivative of (-)-3-acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine.

MS (m/z): 437 (M^+)

^{1}H-NMR ($CDCl_3$, 200 MHz) δ(ppm):

2.14 (3H, s. $-OCOCH_3$), 4.26 (2H. d, J=7.0Hz, $-CH_2OCOCN_3$), 4.45 (1H, dd, J=3.0Hz, 12.0Hz, C_2-H), 4.71 (1H, d, J=12.0Hz, $\overline{C_2}$-H). 4.94 (1H. m, C_3-H), 6.60 (2H. m, aromatic ring proton), 8.73 (2H, d, J=2.0Hz, aromatic ring proton) and 9.19 (1H, t, aromatic ring proton)

EXAMPLE 9

Preparation of (-)-7,8-Difluoro-2,3-Dihydro-3-Hydroxymethyl-4H-[1,4]Benzoxazine (VIII)

In 135 ml of tetrahydrofuran were dissolved 3.03 g of the 3,5-dinitrobenzoyl derivative of (-)-3-acetoxymethyl-7,8-difluoro-2,3-dihydro-4H-[1,4]benzoxazine, and 135 ml of ethanol and 30 ml of 1.0N potassium hydroxide were added to the solution. After the reaction mixture was stirred at room temperature for 30 minutes, 3 ml of acetic acid was added thereto for neutralization. The mixture was concentrated under reduced pressure, and the concentrate was dissolved in 400 ml of chloroform, washed successively with a sodium bicarbonate aqueous solution and water, dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure. The solid was subjected to column chromatography using 40 g of silica gel and eluted with chloroform/methanol (50/1 by volume) to obtain 1.17 g of (-)-7,8-difluoro-2,3-dihydro-3-hydroxymethyl-4H-[1,4]benzoxazine.

$[\alpha]_D^{22}$ = -14.1° (c = 1.80, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 200 MHz) δ (ppm):

3.5 - 4.4 (5H, m), 6.30 - 6.42 (1H, m, aromatic ring proton) and 6.54 - 6.74(1H, m, aromatic ring proton)

EXAMPLE 10

Preparation of (-)-7,8-Difluoro-2,3-Dihydro-3-Methyl-4H-[1,4]Benzoxazine (X')

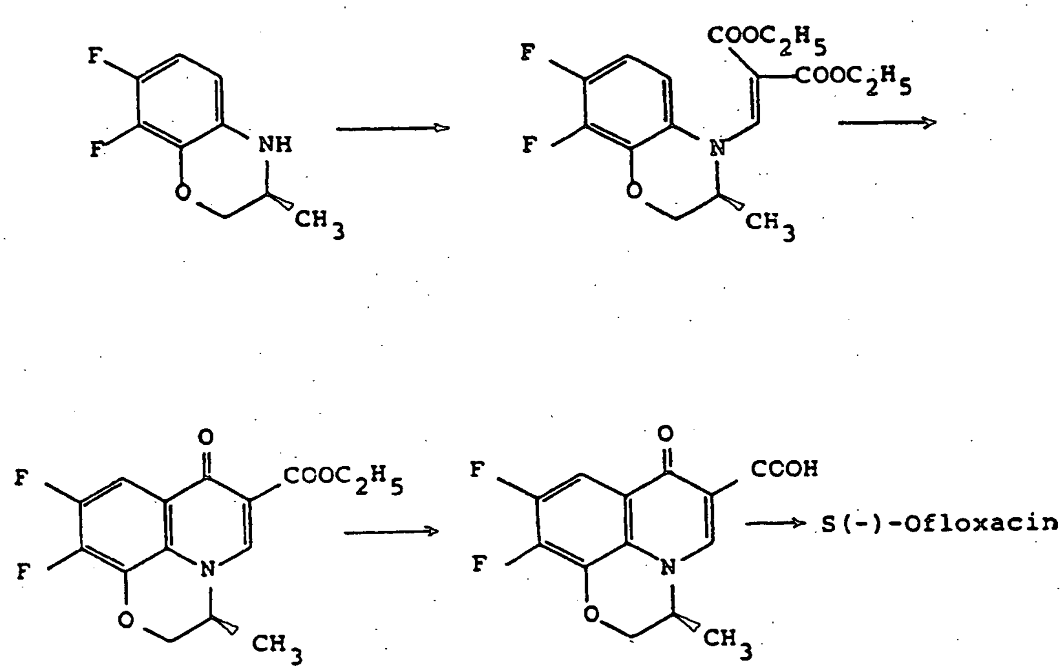
In 20 ml of pyridine was added 1.17 g of (-)-7,8-difluoro-2,3-dihydro-3-hydroxymethyl-4H-[1,4]-benzoxazine, and 2.77 g of thionyl chloride was added thereto dropwise under ice-cooling, followed by stirring at 50 to 60°C for 40 minutes. The reaction mixture was concentrated under reduced pressure, and the concentrate was dissolved in 300 ml of chloroform and washed with 100 ml of a sodium bicarbonate aqueous solution. The washing was extracted twice with 200 ml portions of chloroform. The combined chloroform layers were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The concentrate was subjected to column chromatography using 40 g of silica gel and

eluted with chloroform to obtain 1.18 g of the reaction product as a colorless oily product. This product was dissolved in 30 ml of dimethyl sulfoxide, and 0.41 g of sodium borohydride was added thereto, followed by heating at 80 to 90°C for 1 hour. The reaction mixture was dissolved in 500 ml of benzene, washed with water to remove the dimethyl sulfoxide, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The concentrate was subjected to column chromatography using 40 g of silica gel and eluted with benzene to obtain 0.80 g of (-)-7,8-difluoro-2,3-dihydro-3-methyl-4H-[1,4]benzoxazine as a colorless oily product.
$[\alpha]_D^{25}$ = -9.6° (c = 2.17, $CHCl_3$):
^{1}H-NMR ($CDCl_3$, 200 MHz) δ (ppm):
1.20 (3H, d, J=6.0Hz, $-CH_3$), 3.53 (1H, m, C_3-H), 3.81 (1H, dd, J=8.0Hz, 10.0Hz, C_2-H), 4.31 (1H, dd, J=3.0Hz, 10.0Hz, C_2-H), 6.24 - 6.36 (1H, m, aromatic ring proton) and 6.52 - 6.70 (1H, m, aromatic ring proton)
Optical Purity: >99%e.e.

The product was led to the 3,5-dinitrobenzoyl derivative and quantitatively determined by HPLC using a column of Sumipacks OA-4200; 4.0 x 250 mm and a mixed solvent of n-hexane/1,2-dichloroethane/ethanol (90/9.1/0.9 by volume) at a velocity of 1.5 ml/min.

EXAMPLE 11

Preparation of S(-)-Ofloxacin



To 1.13 g of (-)-7,8-difluoro-2,3-dihydro-3-methyl-4H-[1,4]benzoxazine were added 1.58 g of diethyl ethoxymethylenemalonate, and the mixture was stirred at 130 to 140°C for 70 minutes. The reaction mixture was subjected as such to column chromatography using 50 g of silica gel and eluted with chloroform to obtain 2.47 g of diethyl [(-)-7,8-difluoro-3-methyl-2,3-dihydro-4H-[1,4]benzoxazin-4- yl]-methylenemalonate. This product was dissolved in 5 ml of acetic anhydride, and 10 ml of a mixture of acetic anhydride and concentrated sulfuric acid (2/1 by volume) with stirring under ice-cooling, followed by stirring at 50 to 60°C for 40 minutes. To the reaction mixture were added ice and an aqueous solution of sodium bicarbonate, and the reaction product was extracted three times with 150 ml portions of chloroform. The combined extract was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. When a solid began to precipitate, a small amount of diethyl ether was added thereto, and the precipitate was collected by filtration. The precipitate was washed with a small amount of diethyl

ether to yield 1.32 g of (-)-ethyl 9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]-benzoxazine-6-carboxylate.

In 12 ml of acetic acid were dissolved 1.20 g of the resulting compound, and 25 ml of concentrated hydrochloric acid was added to the solution, followed by refluxing at 120 to 130°C for 90 minutes. Upon allowing the reaction mixture to stand at room temperature, colorless needle-like crystals were precipitated, which were collected by filtration and washed successively with a small amount of water, ethanol and diethyl ether to obtain 0.96 g of (-)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4] benzoxazine-6-carboxylic acid.

In 30 ml of diethyl ether were suspended 324 mg of the resulting compound, and a large excess of boron trifluoride ethyl etherate was added thereto, followed by stirring at room temperature for 30 minutes to form a chelate compound. The product was collected by filtration and washed with a small amount of diethyl ether to obtain 373 mg of a powder. The powder was dissolved in 7 ml of dimethyl sulfoxide, and 136 mg of N-methylpiperazine and 228 mg of triethylamine were added thereto, followed by stirring at room temperature for 17 hours. The reaction mixture was concentrated to dryness under reduced pressure, and to the solid were added 15 ml of 95% methanol and 0.31 ml of triethylamine. The resulting mixture was refluxed for 3 hours. The reaction mixture was concentrated under reduced pressure, and the residue was filtered and washed successively with a small amount of ethanol and diethyl ether to obtain 350 mg of a white powder. Recrystallization from a mixed solvent of ethanol and concentrated aqueous ammonia gave 230 mg of S(-)-Ofloxacin.

Melting Point: 225 - 227°C (with decomposition).

$[\alpha]_D^{23}$ = -76.9° (c = 0.39, 0.05N NaOH)

Ms (m/e): 361 (M^+)

^{1}H-NMR ($CDCl_3$, 200 MHz) δ (ppm):

1.63 (3H, d, C_3-CH_3), 2.38 (3H, s, N-CH_3), 2.54 - 2.60 (4H, m, 2 x CH_2N), 3.40 - 3.44 (4H, m, 2 x $C\underline{H}_2$N), 4.35 - 4.52 (3H, m, C$\underline{H}$ and C$\underline{H}_2$), 7.76 (1H, d, aromatic ring C_8-$\underline{H}$) and 8.64 (1H, s, C_5-$\underline{H}$)

EXAMPLE 12

Preparation of 3S-(+)-7,8-Difluoro-2,3-Dihydro-3-Methyl-4-[(S)-N-para-toluenesulfonylprolyl]-4H-[1,4]-Benzoxazine (X")

A solution of the acid chloride, which was prepared from 61.9 g of (S)-N-p-toluenesulfonylproline and thionyl chloride, in 350 ml of dried dichloromethane was slowly added dropwise to a solution of 32.8 g of (±)-7,8-difluoro-2,3-dihydro-3-methyl-4H-[1,4]benzoxazine and 28 ml of pyridine in 300 ml of dried dichloromethane at room temperature under stirring. The stirring was further continued for an additional 4 hours at room temperature. The reaction mixture was washed successively with 10% hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The dichloromethane was removed by distillation, and the oily residue was dissolved in 200 ml of ethyl acetate. To the solution were slowly added dropwise 750 ml of n-hexane while stirring whereby crystals ((-)-isomer of the compound (X") wherein X_1 = X_2 = F; R_1 = CH_3; R_2 = p-toluenesulfonyl; and n = 1) precipitated immediately. The precipitated crystals were separated by filtration, and the filtrate was concentrated to dryness under reduced pressure. The residue was subjected to column chromatography using 500 g of silica gel and eluted with benzene/ethyl acetate (50/1 - 25/1 by volume) to obtain an oily product. The oily product was dissolved in 500 ml of ethanol, and the solution was allowed to stand at room temperature for 1 day, thereby to precipitate crystals. The ethanol was distilled off, and to the thus recovered crystals were added diethyl ether and n-hexane, followed by filtration. The solid was dried under reduced pressure to obtain 33.4 g of 3S-(+)-7,8-difluoro-2,3-dihydro-3-methyl-4-[(S)-N-p-toluenesulfonylprolyl]-4H-[1,4]benzoxazine ((+)-isomer of the compound (X") wherein X_1 = X_2 = F; R_1 = CH_3; R_2 = p-toluenesulfonyl; and n = 1) having a melting point of 107 - 108°C.

$[\alpha]_D$ = +70.7° (c = 0.953, chloroform)

$$IR\ \nu_{max}^{KBr}(cm^{-1}):$$

1685, 1510, 1490

Elementary Analysis for $C_{21}H_{22}F_2N_2O_4S$:			
Calcd. (%):	C 57.79,	H 5.08,	N 6.42
Found (%):	C 58.05,	H 5.14,	N 6.47

EXAMPLE 13

Preparation of S-(-)-7,8-Difluoro-2,3-Dihydro-3-Methyl-4H-[1,4]Benzoxazine (X)

In 1 liter of ethanol were dissolved 32.8 g of the (+)-isomer as obtained in Example 12, and 300 ml of 1N sodium hydroxide were added thereto, followed by refluxing for 3 hours. The ethanol was removed by distillation, and the oily residue was extracted with benzene. The extract was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate and distilled to remove benzene. The residue was subjected to column chromatography using 200 g of silica gel as a carrier and benzene as an eluent to obtain 12.7 g (yield: 91.4%) of S-(-)-7,8-difluoro-2,3-dihydro-3-methyl-4H-[1,4]benzoxazine as an oily product.
$[\alpha]_D$ = -9.6° (c = 2.17, chloroform)

The absolute configuration of this compound was decided to be S-configuration by X-ray analysis on its hydrochloride.

EXAMPLE 14

Preparation of Ethyl (S)-(-)-9,10-Difluoro-3-Methyl-7-Oxo-2,3-Dihydro-7H-Pyrido[1,2,3-de][1,4]Benzoxazine-6-Carboxylate (XII)

To 15.8 g of the (S)-(-)-benzoxazine derivative as obtained in Example 13 were added 24.0 g of diethyl ethoxymethylenemalonate, and the mixture was stirred at 130 to 140°C for 1 hour under reduced pressure. After cooling, the reaction mixture was dissolved in 50 ml of acetic anhydride, and 80 ml of a mixture of acetic anhydride and concentrated sulfuric acid (2:1 by volume) was slowly added dropwise to the solution while stirring under ice-cooling. After continuing the stirring for additional one hour at room temperature, the reaction mixture was stirred in a hot bath of 50 to 60°C for 30 minutes. Ice-water was added to the reaction mixture, and powdery potassium carbonate was added thereto for neutralization. The mixture was extracted with chloroform, and the extract was washed successively with a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride and dried over sodium sulfate. The chloroform was removed by distillation, and to the residue was added diethyl ether. The crystals thus formed were collected by filtration to give 20.0 g of the title compound having a melting point of 257 - 258°C.
$[\alpha]_D$ = -68.1° (c = 0.250, acetic acid)

EXAMPLE 15

Preparation of S-(-)-9,10-Difluoro Methyl-7-Oxo-2,3-Dihydro-7H-Pyrido[1,2,3-de][1,4]Benzoxazine-6-Carboxylic Acid

In 150 ml of acetic acid were dissolved 19.5 g of the ester compound obtained in Example 14, and 400 ml of concentrated hydrochloric acid were added thereto, followed by refluxing for 3 hours. After cooling, the precipitated crystals were collected by filtration, washed successively with water, ethanol and diethyl ether and dried to obtain 16.2 g of the corresponding carboxylic acid having a melting point of 300°C or higher.
$[\alpha]_D$ = -65.6° (c = 0.985, DMSO)

EXAMPLE 16

Preparation of S-(-)-9-Fluoro-3-Methyl-10-(4-Methyl-1-Piperazinyl)-7-oxo-2,3-Dihydro-7H-Pyrido[1,2,3-de]-[1,4]Benzoxazine-6-Carboxylic Acid (VI) (S-(-)-Isomer of Ofloxacin)

In 600 ml of diethyl ether were suspended 14.3 g of the carboxylic acid obtained in Example 15, and 70

ml of boron trifluoride diethyl etherate were added thereto, followed by stirring at room temperature for 5 hours. The supernatant liquid was removed by decantation, and to the residue was added diethyl ether, followed by filtration. The solid was washed with diethyl ether and dried. The product was dissolved in 100 ml of dimethyl sulfoxide, and 14.2 ml of triethylamine and 7.3 ml of N-methylpiperazine were added to the solution. After the mixture was stirred at room temperature for 18 hours, the solvent was removed by distillation. Diethyl ether was added to the residue, followed by filtration. The collected yellow powder was suspended in 400 ml of 95% methanol, and 25 ml of triethylamine was added thereto. The mixture was heated at reflux for 25 hours. The solvent was distilled off under reduced pressure, and the residue was dissolved in 500 ml of 10% hydrochloric acid and washed three times with chloroform. The washed solution was adjusted to a pH of 11 with a 4N sodium hydroxide aqueous solution and then to a pH of 7.3 with 1N hydrochloric acid. The solution was extracted three times with 2 liter portions of chloroform, and the combined extract was dried over sodium sulfate. The chloroform was removed by distillation, and the resulting crystal was recrystallized from ethanol/diethyl ether to obtain 12.0 g of the title compound having a melting point of 226 - 230 °C (with decomposition).

$[\alpha]_D$ = -76.9° (c = 0.655, 0.05N NaOH)

EXAMPLE 17

Preparation of (S)-(-)-9-Fluoro-3-Methyl-10-(4-Ethyl-1-Piperaziny1)-7-Oxo-2,3-Dihydro-7H-Pyrido[1,2,3-de]-[1,4]Benzoxazine-6-Carboxylic Acid (VI)

In the same manner as described in Example 16 except that N-ethylpiperazine was used in place of N-methylpiperazine, the titled compound was obtained having a melting point of 229 - 230 °C (with decomposition).

Elementary Analysis for $C_{19}H_{22}FN_3O_4$:			
Calcd. (%):	C 60.79	H 5.91	N 11.19
Found (%):	C 60.97	H 5.91,	N 11.30

$[\alpha]_D$ = -67.0° (c = 0.585, H_2O)
NMR ($CDCl_3$) δ (ppm):

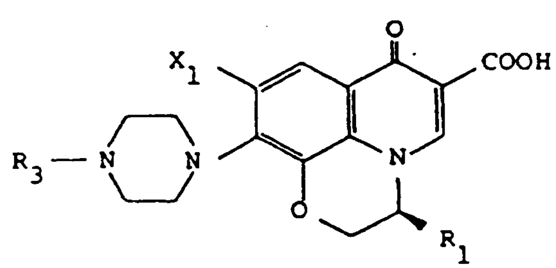
1.16 (3H, t, J=7Hz, -CH_2<u>CH_3</u>), 1.63 (3H, d, J=7Hz, CH_3), 2.53 (2H, q, J=7Hz, <u>CH_2</u>CH_3), 2.57 - 2.69 (4H, m, 2 x CH_2), 3.40 - 3.53 (4H, m, 2 x CH_2), 4,32 - 4.58 (3H, m, CH and CH_2), 7.77 (1H, d, J=12Hz, C_8-H), 8.67 (1H, S, C_5-H)

While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

Claims

Claims for the following Contracting States : DE, GB, FR, IT, NL, SE, LI, CH, BE

1. An S(-)-pyridobenzoxazine compound represented by the formula (VI)



(VI)

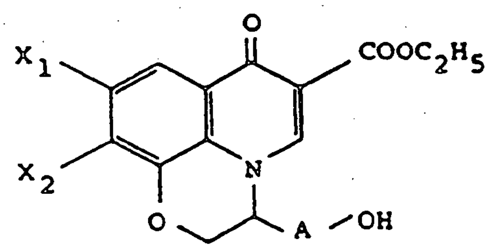
wherein X_1 represents a fluorine atom, R_1 represents a methyl group, and R_3 represents a methyl or an ethyl group.

2. S(-)-9-Fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]-benzoxazine-6-carboxylic acid according to claim 1.

3. S(-)-9-Fluoro-3-methyl-10-(4-ethyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid according to claim 1.

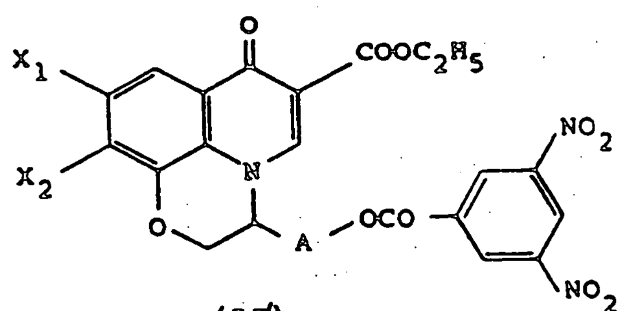
4. Process for producing the S-(-)-Pyridobenzoxazines of the formula VI according to claims 1 - 3,

characterized in that
A) one treats a compound of the general formula I'



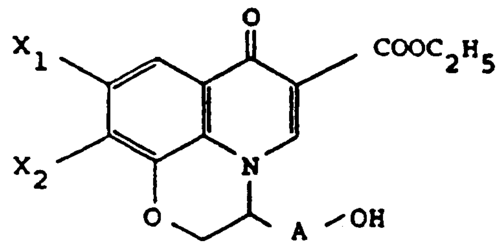
(±) (I')

wherein X_1 has the meaning given in claim 1, X_2 represents a halogen atom, and
A represents a methylene group,
with 3,5-dinitrobenzoylchloride to give the (±)-3,5-dinitrobenzoate of the general formula II'



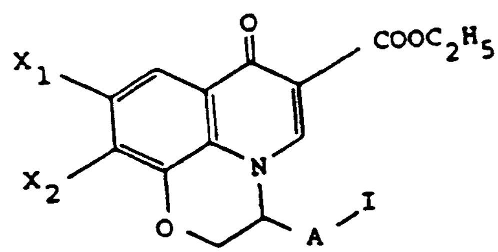
(II')

optically resolves the thus obtained compound of the general formula II' to give the S-(-)-compound and selectively hydrolyzes the benzoate moiety to give the hydroxymethylene compound of the general formula III'



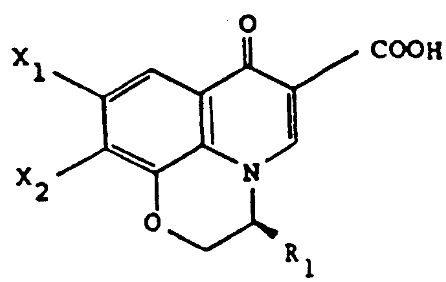
III'

converts the thus obtained compound with a iodinating reagent to give the 3-iodomethylene compound of the general formula IV'



(IV')

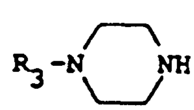
reduces the thus obtained compound of the general formula IV' to give the 3-methyl compound and hydrolyzes it under acidic conditions to give the 3-methyl-6-carboxylic acid compound of the general formula V



(V)

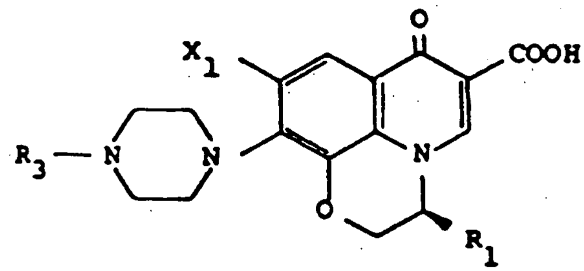
wherein R_1 has the meanings given in claim 1, and

reacts the thus obtained compound with an N-alkylpiperazine of the following formula



wherein R_3 has the meanings given in claim 1,

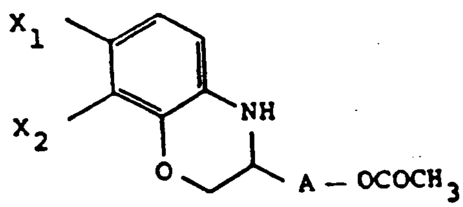
to give a compound of the general formula VI



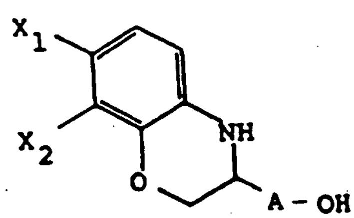
(VI)

or

B) reacts a 7,8-dihalogeno-2,3-dihydro-3-acetoxymethylene-4H-[1,4]benzoxazine of the general formula VII' with an asymmetric hydrolytic enzyme to recover a mixture comprising the starting compound VII' rich in either one of optical isomers and a 3-hydroxymethylene compound VIII'



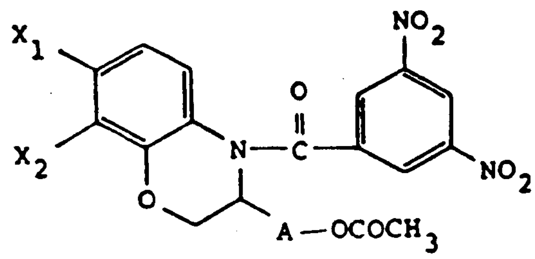
(VII)



(VIII')

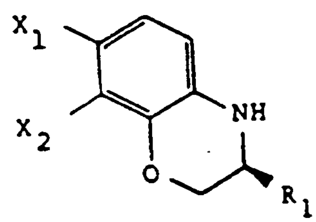
wherein A has the meanings given above, separates the mixture into each compound,

dinitrobenzoylates either one or both of these compounds and further acetylates the benzoylated 3-hydroxymethylene compound VIII' to obtain the compound of the general IX'



(IX)

separates the compound into the optical isomers by cristallization, subjects the resulting 3-(-)-isomer to deacylation and dehydroxylation by means of known chemical processes to obtain an optically active 7,8-dihalogeno-2,3-dihydro-3-alkyl-4H-[1,4]benzoxazine (X)

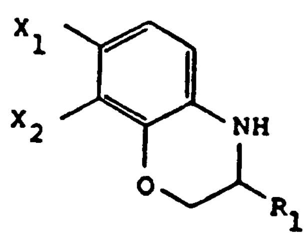


(X)

wherein X_1, X_2 and R_1 have the meanings given above, and

obtains therefrom as described in process C an optically active compound of the general formula VI, or

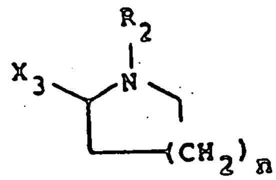
C) condenses a 7,8-dihalogeno-1,4-benzoxazine derivative of the general formula (X')



(X')

wherein X_1, X_2 and R_1 have the meanings given above,

with a cyclic amino acid or a reactive derivative thereof of the general formula XIV



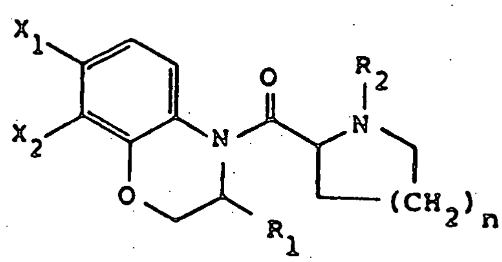
(XIV)

wherein R_2 represents a substituted sulfonyl group, an alkoxy carbonyl group or an aralkoxy carbonyl group,

n represents an integer of 1 to 3, and

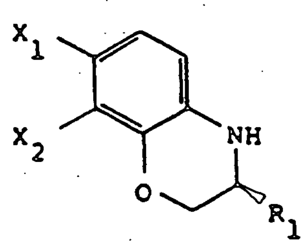
X_3 represents a carboxyl group or a reactive derivative thereof,

to produce a compound of the general formula X"



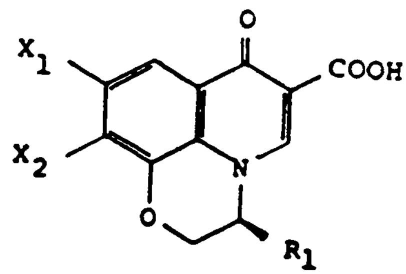
(X")

separates the diastomeric mixture of the obtained compound of the general formula X" and hydrolyzes the thus separated diastereomer to give a 7,8-dihalogeno-3-(S)-methyl-[1,4]-benzoxazine of the general formula (X)



(X)

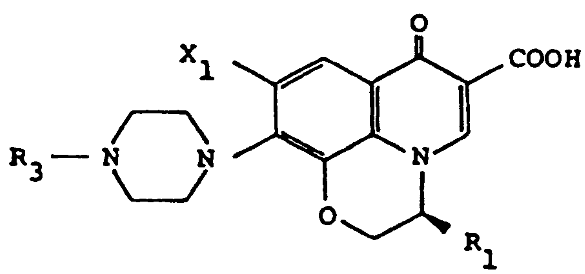
reacts the thus obtained compound by known reactions to give a 9,10-dihalogeno-3-(S or R)-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid of the general formula (V)



(V)

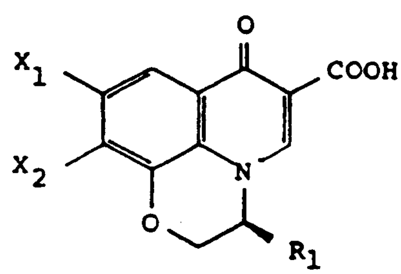
and
converts the thus obtained compound as described in process A) to a compound of the general formula VI.

5. A process for preparing an S(-) - pyridobenzoxazine compound represented by the formula (VI)



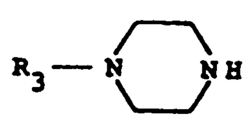
VI

wherein X_1 represents a fluorine atom, R_1 represents a methyl group, and R_3 represents a methyl group or an ethyl group, which comprises reacting an S(-) - 9 - fluoro - 10 - halogeno - pyridobenzoxazine compound represented by the formula (V) or the reaction product thereof with borontrifluoride,



V

wherein X_1 and R_1 have the meanings given above, and X_2 represents a halogen atom, with an N - alkyl - piperazine represented by the following formula



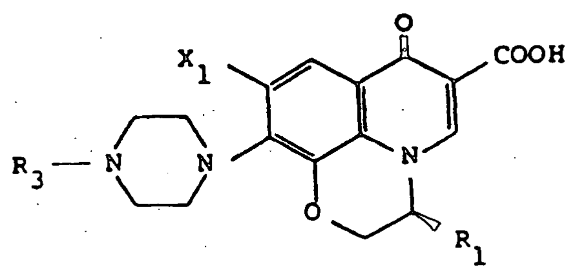
wherein R_3 has the meanings given above.

6. Pharmaceutical composition, containing at least one compound of claims 1 to 3, optionally together with a common carrier and/or diluent.

7. The use of at least one compound according to any one of claims 1 to 3 for preparing an antimicrobially active pharmaceutical composition.

Claims for the following Contracting State : AT

1. A process for producing an S(-)-pyridobenzoxazine compound represented by the formula (VI)

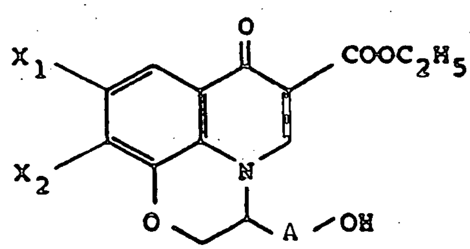


(VI)

wherein X_1 represents a fluorine atom, R_1 represents a methyl group, and R_3 represents a methyl or an ethyl group.

characterized in that

A) one treats a compound of the general formula I'

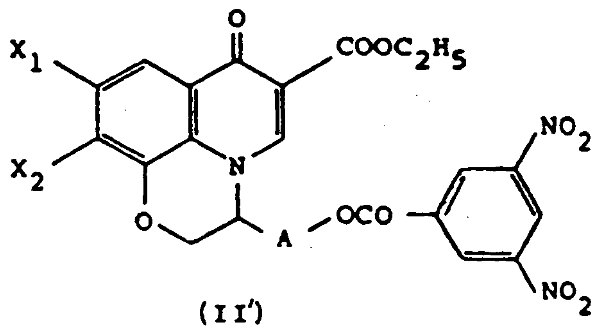


(±) (I')

wherein X_1 has the meaning given above, X_2 represents a halogen atom, and

A represents a methylene group,

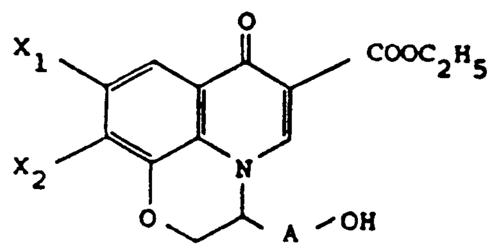
with 3,5-dinitrobenzoylchloride to give the (±)-3,5-dinitrobenzoate of the general formula II'



(II')

,

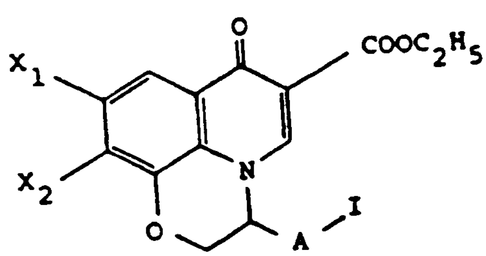
optically resolves the thus obtained compound of the general formula II' to give the S-(-)-compound and selectively hydrolyzes the benzoate moiety to give the hydroxymethylene compound of the general formula III'



III'

,

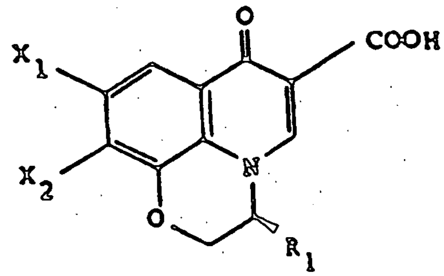
converts the thus obtained compound with a iodinating reagent to give the 3-iodomethylene compound of the general formula IV'



(IV')

,

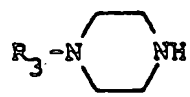
reduces the thus obtained compound of the general formula IV' to give the 3-methyl compound and hydrolyzes it under acidic conditions to give the 3-methyl-6-carboxylic acid compound of the general formula V



(V)

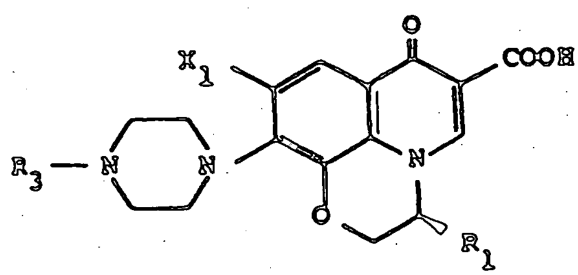
wherein R_1 has the meanings given above, and

reacts the thus obtained compound with an N-alkylpiperazine of the following formula



wherein R_3 has the meanings given above,

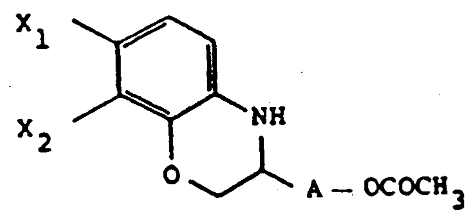
to give a compound of the general formula VI



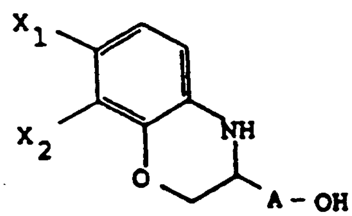
(VI)

or

B) reacts a 7,8-dihalogeno-2,3-dihydro-3-acetoxymethylene-4H-[1,4]benzoxazine of the general formula VII' with an asymmetric hydrolytic enzyme to recover a mixture comprising the starting compound VII' rich in either one of optical isomers and a 3-hydroxymethylene compound VIII'



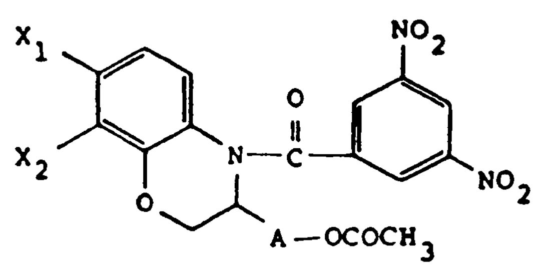
(VII')



(VIII')

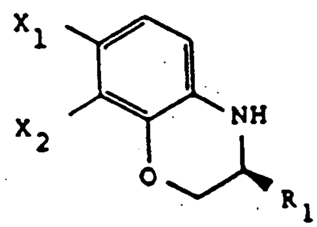
wherein A has the meanings given above, separates the mixture into each compound,

dinitrobenzoylates either one or both of these compounds and further acetylates the benzoylated 3-hydroxymethylene compound VIII' to obtain the compound of the general IX'



(IX')

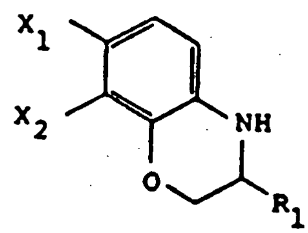
separates the compound into the optical isomers by cristallization,
subjects the resulting 3-(-)-isomer to deacylation and dehydroxylation by means of known chemical processes to obtain an optically active 7,8-dihalogeno-2,3-dihydro-3-alkyl-4H-[1,4]benzoxazine (X)



(X)

wherein X_1, X_2 and R_1 have the meanings given above, and

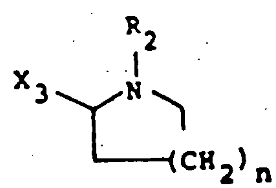
obtains therefrom as described in process C an optically active compound of the general formula VI, or
C) condenses a 7,8-dihalogeno-1,4-benzoxazine derivative of the general formula (X')



(X')

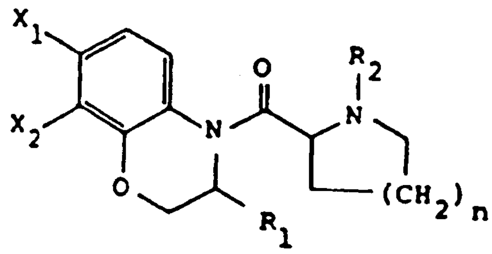
wherein X_1, X_2 and R_1 have the meanings given above,

with a cyclic amino acid or a reactive derivative thereof of the general formula XIV



(XIV)

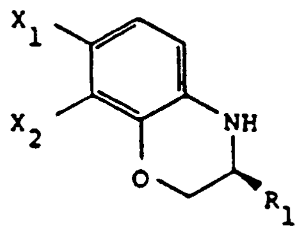
wherein R_2 represents a substituted sulfonyl group, an alkoxy carbonyl group or an aralkoxy carbonyl group,
n represents an integer of 1 to 3, and
X_3 represents a carboxyl group or a reactive derivative thereof,
to produce a compound of the general formula X"



(X")

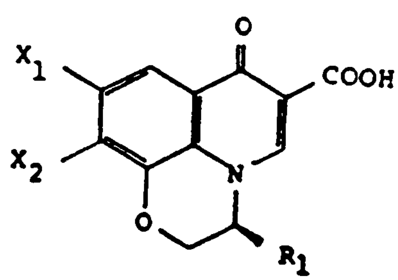
,

separates the diastomeric mixture of the obtained compound of the general formula X" and hydrolyzes the thus separated diastereomer to give a 7,8-dihalogeno-3-(S)-methyl-[1,4]-benzoxazine of the general formula (X)



(X)

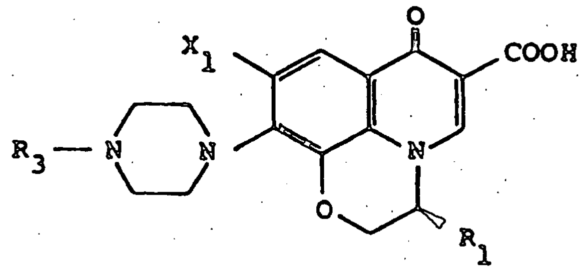
reacts the thus obtained compound by known reactions to give a 9,10-dihalogeno-3-(S or R)-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid of the general formula (V)



(V)

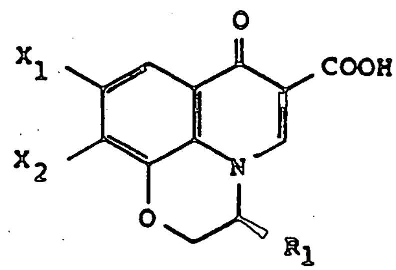
and
converts the thus obtained compound as described in process A) to a compound of the general formula VI.

2. A process for preparing an S(-) - pyridobenzoxazine compound represented by the formula (VI)



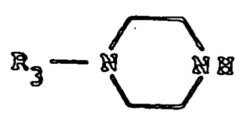
VI

wherein X_1 represents a fluorine atom, R_1 represents a methyl group, and R_3 represents a methyl group or an ethyl group, which comprises reacting an S(-) - 9 - fluoro - 10 - halogeno - pyridobenzoxazine compound represented by the formula (V) or the reaction product thereof with borontrifluoride,



V

wherein X_1 and R_1 have the meanings given above, and X_2 represents a halogen atom, with an N - alkyl - piperazine represented by the following formula



wherein R_3 has the meanings given above.

3. The process of claim 1 or 2, wherein the compound obtained is S(-)-9-Fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]-benzoxazine-6-carboxylic acid.

4. The process of claim 1 or 2, wherein the compound obtained is S(-)-9-Fluoro-3-methyl-10-(4-ethyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]-benzoxazine-6-carboxylic acid.

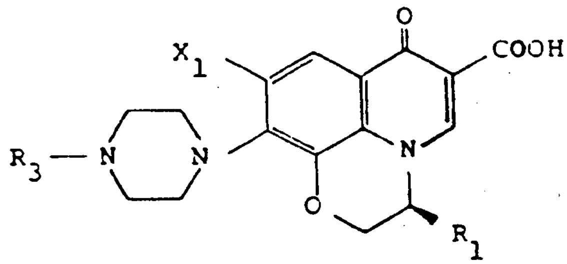
5. A process for preparing a pharmaceutical composition which comprises providing at least one compound of formula VI as defined in claims 1 to 4 in a form suitable for administration, optionally incorporated into a common carrier and/or diluent.

6. The use of at least one compound of formula VI as defined in claims 1 to 4 for preparing a antibacterially active pharmaceutical composition.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, NL, SE

1. S(-)-Pyridobenzoxazin-Verbindungen der Formel (VI)



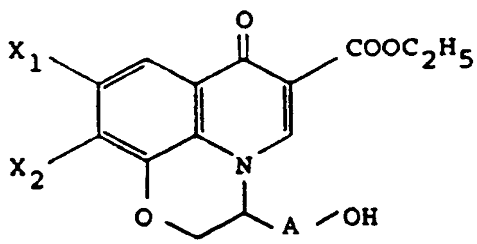
(VI)

worin X_1 für ein Fluoratom steht, R_1 eine Methylgruppe und R_3 eine Methyl- oder eine Ethylgruppe darstellt.

2. S(-)-9-Fluor-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazin-6-carbonsäure gemäß Anspruch 1.

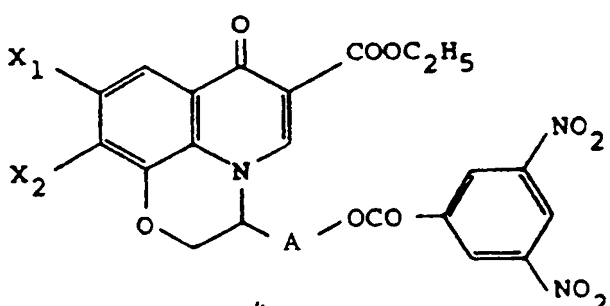
3. S(-)-9-Fluor-3-methyl-10-(4-ethyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazin-6-carbonsäure gemäß Anspruch 1.

4. Verfahren zur Herstellung der S-(-)-Pyridobenzoxazine der Formel VI nach den Ansprüchen 1-3, dadurch gekennzeichnet, daß man
A) eine Verbindung der allgemeinen Formel I'



(±) (I')

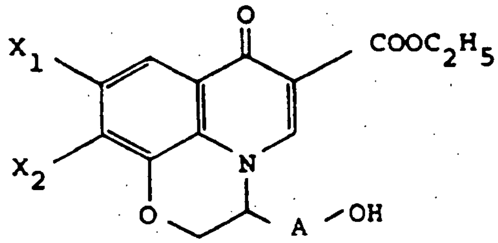
worin X_1 wie in Anspruch 1 definiert ist, X_2 für ein Halogenatom steht und A für eine Methylengruppe steht, mit 3,5-Dinitrobenzoylchlorid behandelt, wobei man das (±)-3,5-Dinitrobenzoat der allgemeinen Formel II'



(II')

erhält,

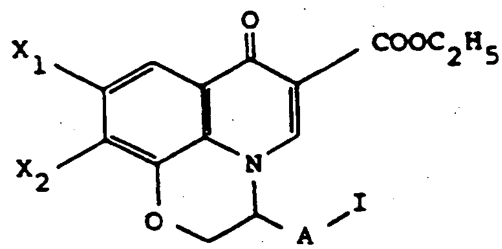
die so erhaltene Verbindung der allgemeinen Formel II' optisch auflöst, wobei man die S-(-)-Verbindung erhält, und den Benzoatrest selektiv hydrolysiert, wobei man die Hydroxymethylenverbindung der allgemeinen Formel III'



III'

erhält,

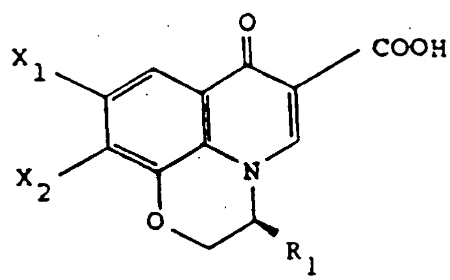
die so erhaltene Verbindung mit einem Jodierungsreagens in die 3-Jodmethylenverbindung der allgemeinen Formel IV'



(IV')

umwandelt,

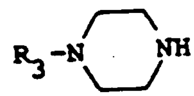
die so erhaltene Verbindung der allgemeinen Formel IV' reduziert, wobei man die 3-Methylverbindung erhält, und diese unter sauren Bedingungen hydrolysiert, wobei man die 3-Methyl-6-carbonsäureverbindung der allgemeinen Formel V



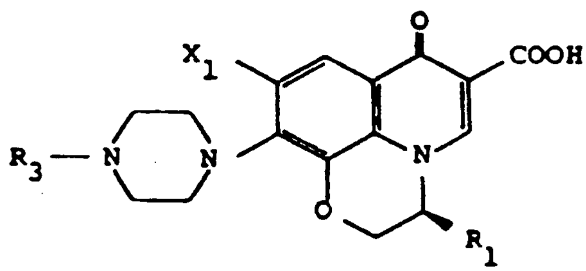
(V)

worin R_1 wie in Anspruch 1 definiert ist, erhält, und

die so erhaltene Verbindung mit einem N-Alkylpiperazin der folgenden Formel



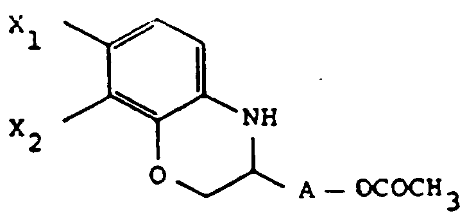
worin R_3 wie in Anspruch 1 definiert ist, umsetzt, wobei man eine Verbindung der allgemeinen Formel VI



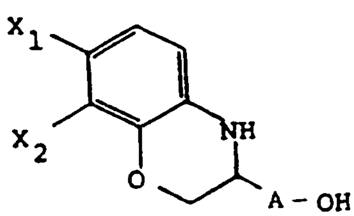
(VI)

erhält, oder

B) ein 7,8-Dihalogen -2,3-dihydro-3-acetoxymethylen-4H-[1,4]benzoxazin der allgemeinen Formel VII' mit einem asymetrischen hydrolytischen Enzym umsetzt, wobei man ein Gemisch erhält, das die mit einem der optischen Isomeren angereicherte Ausgangsverbindung VII' und eine 3-Hydroxymethylen-verbindung VIII'



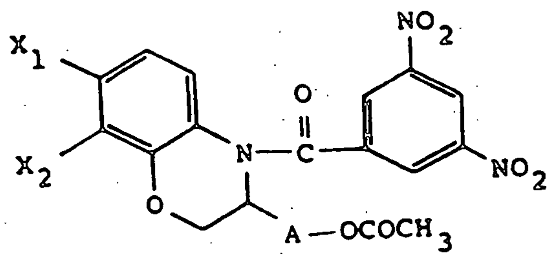
(VII')



(VIII')

worin A wie oben definiert ist, enthält,

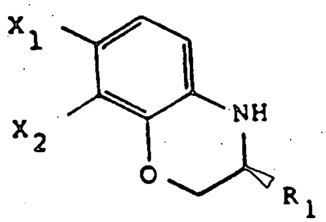
das Gemisch in beide Verbindungen auftrennt, entweder eine oder beide dieser Verbindungen dinitrobenzoyliert und die benzoylierte 3-Hydroxymethylenverbindung VIII' weiter acetyliert, wobei man die Verbindung der allgemeinen Formel IX'



(IX')

erhält,

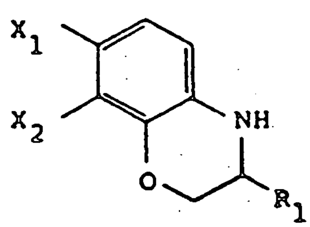
die Verbindung durch Kristallisation in die optischen Isomere auftrennt, das so erhaltene 3-(-)-Isomer nach bekannten chemischen Verfahren deacyliert und dehydroxyliert, wobei man ein optisch aktives 7,8-Dihalogen-2,3-dihydro-3-alkyl-4H-[1,4]benzoxazin (X)



(X)

worin X_1, X_2 und R_1 wie oben definiert sind, erhält, und daraus, wie in Verfahren C beschrieben, eine optisch aktive Verbindung der Formel VI erhält, oder

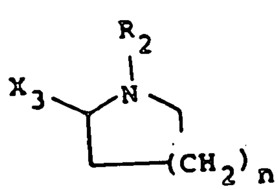
C) ein 7,8-Dihalogen -1,4-benzoxazinderivat der allgemeinen Formel (X')



(X')

worin X_1, X_2 und R_1 wie oben definiert sind, kondensiert

mit einer cyclischen Aminosäure oder einem reaktiven Derivat davon der allgemeinen Formel XIV

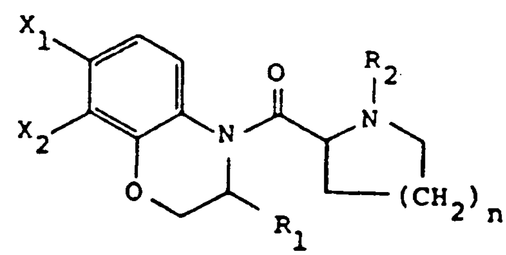


(XIV)

worin R_2 eine substituierte Sulfonylgruppe, eine Alkoxycarbonylgruppe oder eine Aralkoxycarbonylgruppe darstellt,

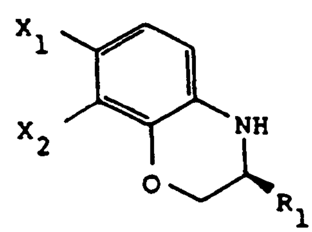
n für eine ganze Zahl von 1 bis 3 steht, und
X_3 für eine Carboxylgruppe oder ein reaktives Derivat davon steht,

wobei man eine Verbindung der allgemeinen Formel X"



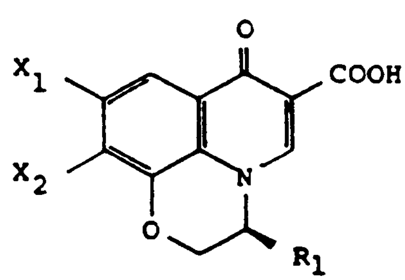
(X")

erhält,
das Diastereomerengemisch der erhaltenen Verbindung der allgemeinen Formel X" trennt und das so erhaltene, getrennte Diastereomer hydrolysiert, wobei man ein 7,8-Dihalogen-3-(S)-methyl-[1,4]-benzoxazin der allgemeinen Formel (X)



(X)

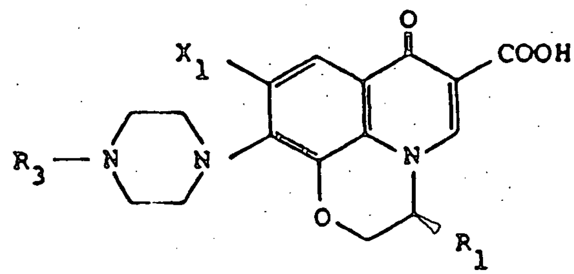
erhält,
die so erhaltene Verbindung anhand von bekannten Reaktionen zu einer 9,10-Dihalogen-3-(S oder R)-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]-benzoxazin-6-carbonsäure der allgemeinen Formel (V)



(V)

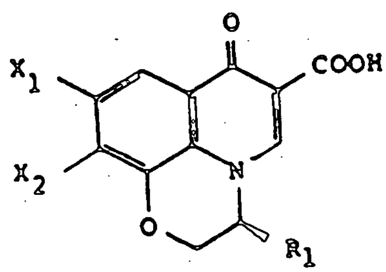
umsetzt, und
die so erhaltene Verbindung wie in Verfahren A) beschrieben in eine Verbindung der allgemeinen Formel VI umwandelt.

5. Verfahren zur Herstellung einer S(-)-Pyridobenzoxazinverbindung der Formel (VI)



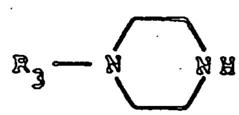
VI

worin X_1 ein Fluoratom darstellt, R_1 für eine Methylgruppe und R_3 für eine Methyl- oder Ethylgruppe steht, wobei man eine S(-)-9-Fluor-10-Halogenpyridobenzoxazinverbindung der Formel (V)



V

worin X_1 und R_1 wie oben definiert sind und X_2 für ein Halogenatom steht, oder das Reaktionsprodukt davon mit Borontrifluorid mit einem N-Alkyl-piperazin der folgenden Formel



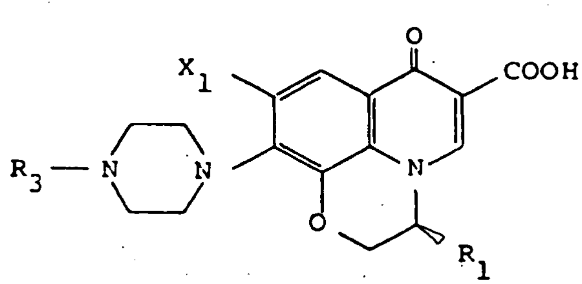
worin R_3 wie oben definiert ist, umsetzt.

6. Pharmazeutisches Mittel, enthaltend mindestens eine Verbindung der Ansprüche 1 bis 3, gegebenenfalls zusammen mit einem üblichen Träger und/oder Diluens.

7. Verwendung mindestens einer Verbindung nach einem der Ansprüche 1 bis 3 zur Herstellung eines antimikrobiell wirksamen pharmazeutischen Mittels.

Patentansprüche für folgende Vertragsstaat : AT

1. Verfahren zur Herstellung von S(-)-Pyridobenzoxazin-Verbindungen der Formel (VI)

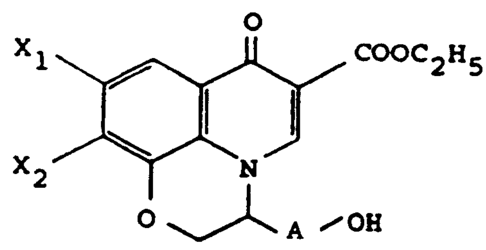


(VI)

worin X_1 für ein Fluoratom steht, R_1 eine Methylgruppe und R_3 eine Methyl- oder eine Ethylgruppe darstellt,

dadurch gekennzeichnet, daß man

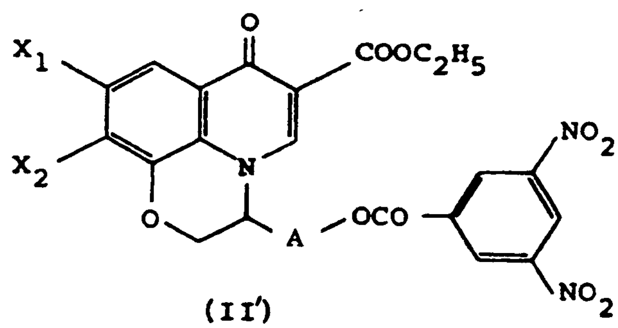
A) eine Verbindung der allgemeinen Formel I'



(±) (I')

worin X_1 wie oben definiert ist, X_2 für ein Halogenatom steht und A für eine Methylengruppe steht,

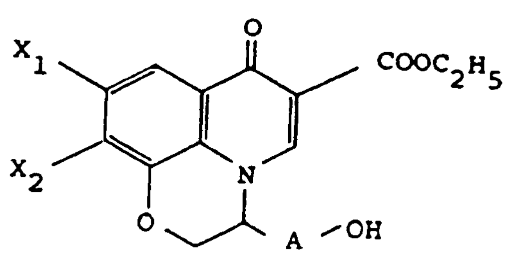
mit 3,5-Dinitrobenzoylchlorid behandelt, wobei man das (±)-3,5-Dinitrobenzoat der allgemeinen Formel II'



(II')

erhält,

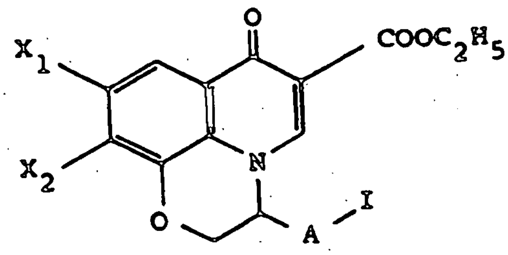
die so erhaltene Verbindung der allgemeinen Formel II' optisch auflöst, wobei man die S-(-)-Verbindung erhält, und den Benzoatrest selektiv hydrolysiert, wobei man die Hydroxymethylenverbindung der allgemeinen Formel III'



III'

erhält,

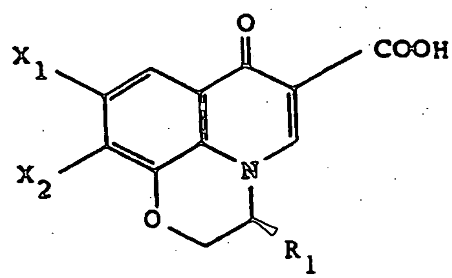
die so erhaltene Verbindung mit einem Jodierungsreagens in die 3-Jodmethylenverbindung der allgemeinen Formel IV'



(IV')

umwandelt,

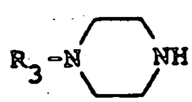
die so erhaltene Verbindung der allgemeinen Formel IV' reduziert, wobei man die 3-Methylverbindung erhält, und diese unter sauren Bedingungen hydrolysiert, wobei man die 3-Methyl-6-carbonsäureverbindung der allgemeinen Formel V



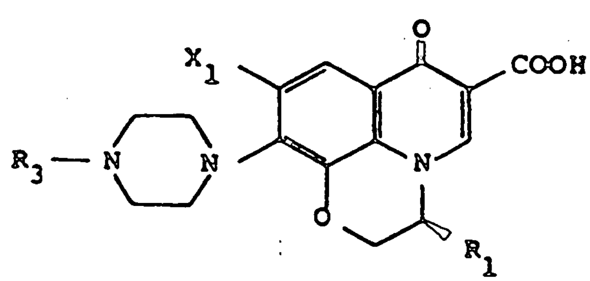
(V)

worin R_1 wie oben definiert ist, erhält, und

die so erhaltenen Verbindung mit einem N-Alkylpiperazin der folgenden Formel



worin R_3 wie oben definiert ist, umsetzt, wobei man eine Verbindung der allgemeinen Formel VI

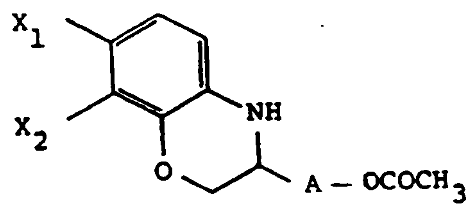


(VI)

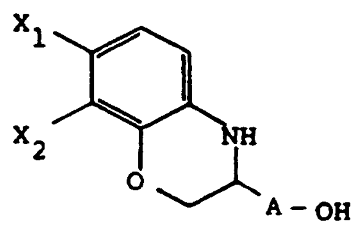
erhält, oder

B) ein 7,8-Dihalogen -2,3-dihydro-3-acetoxymethylen-4H-[1,4]benzoxazin der allgemeinen Formel VII'

mit einem asymetrischen hydrolytischen Enzym umsetzt, wobei man ein Gemisch erhält, das die mit einem der optischen Isomeren angereicherte Ausgangsverbindung VII' und eine 3-Hydroxymethylenverbindung VIII'



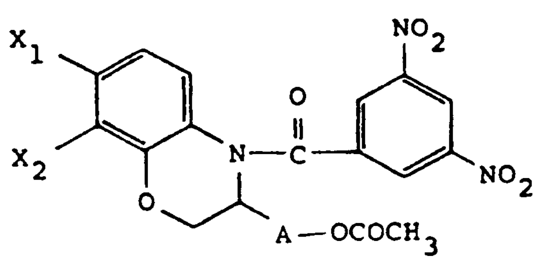
(VII')



(VIII')

worin A wie oben definiert ist, enthält,

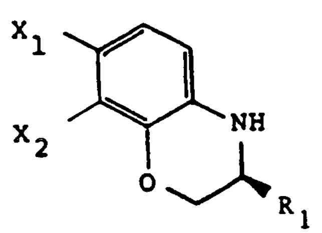
das Gemisch in beide Verbindungen auftrennt, entweder eine oder beide dieser Verbindungen dinitrobenzoyliert und die benzoylierte 3-Hydroxymethylenverbindung VIII' weiter acetyliert, wobei man die Verbindung der allgemeinen Formel IX'



(IX')

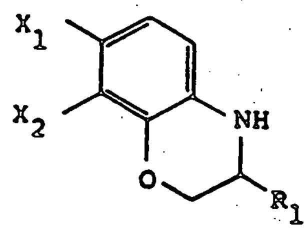
erhält,

die Verbindung durch Kristallisation in die optischen Isomere auftrennt,
das so erhaltene 3-(-)-Isomer nach bekannten chemischen Verfahren deacyliert und dehydroxyliert, wobei man ein optisch aktives 7,8-Dihalogen-2,3-dihydro-3-alkyl-4H-[1,4]benzoxazin (X)



(X)

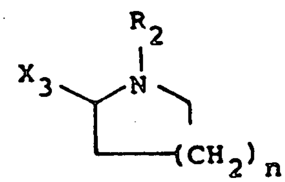
worin X_1, X_2 und R_1 wie oben definiert sind, erhält, und daraus, wie in Verfahren C beschrieben, eine optisch aktive Verbindung der Formel VI erhält, oder
C) ein 7,8-Dihalogen -1,4-benzoxazinderivat der allgemeinen Formel (X')



(X')

worin X_1, X_2 und R_1 wie oben definiert sind, kondensiert

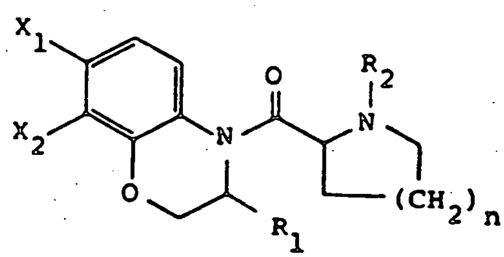
mit einer cyclischen Aminosäure oder einem reaktiven Derivat davon der allgemeinen Formel XIV



(XIV)

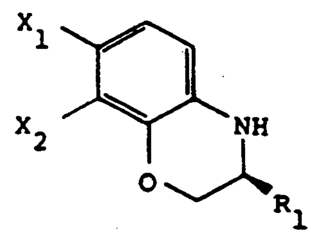
worin R_2 eine substituierte Sulfonylgruppe, eine Alkoxycarbonylgruppe oder eine Aralkoxycarbonylgruppe darstellt,
n für eine ganze Zahl von 1 bis 3 steht, und
X_3 für eine Carboxylgruppe oder ein reaktives Derivat davon steht,

wobei man eine Verbindung der allgemeinen Formel X"



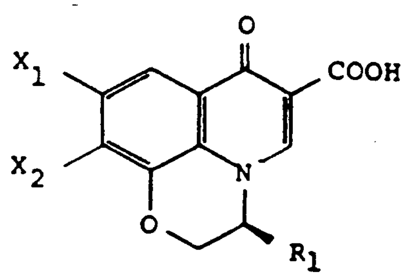
(X")

erhält,
das Diastereomerengemisch der erhaltenen Verbindung der allgemeinen Formel X" trennt und das so erhaltene, getrennte Diastereomer hydrolysiert, wobei man ein 7,8-Dihalogen-3-(S)-methyl-[1,4]-benzoxazin der allgemeinen Formel (X)



(X)

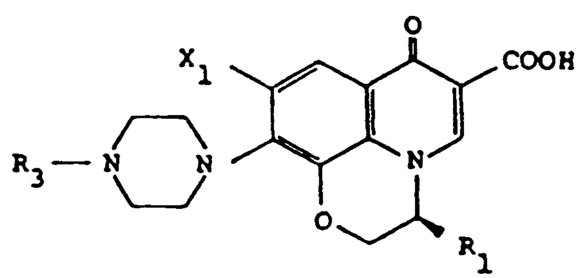
erhält,
die so erhaltene Verbindung anhand von bekannten Reaktionen zu einer 9,10-Dihalogen-3-(S oder R)-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]-benzoxazin-6-carbonsäure der allgemeinen Formel (V)



(V)

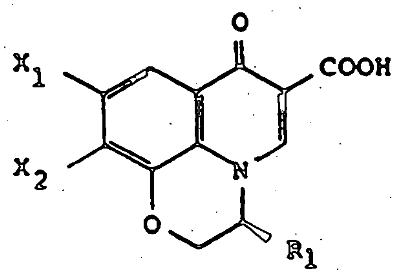
umsetzt, und
die so erhaltene Verbindung wie in Verfahren A) beschrieben in eine Verbindung der allgemeinen Formel VI umwandelt.

2. Verfahren zur Herstellung einer S(-)-Pyridobenzoxazinverbindung der Formel (VI)



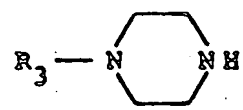
VI

worin X_1 ein Fluoratom darstellt, R_1 für eine Methylgruppe und R_3 für eine Methyl- oder Ethylgruppe steht, wobei man eine S(-)-9-Fluor-10-Halogenpyridobenzoxazinverbindung der Formel (V)



V

worin X_1 und R_1 wie oben definiert sind und X_2 für ein Halogenatom steht, oder das Reaktionsprodukt davon mit Borontrifluorid mit einem N-Alkyl-piperazin der folgenden Formel



worin R_3 wie oben definiert ist, umsetzt.

3. Verfahren nach Anspruch 1 oder 2, worin die erhaltene Verbindung S(-)-9-Fluor-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazin-6-carbonsäure ist.

4. Verfahren nach Anspruch 1 oder 2, worin die erhaltene Verbindung S(-)-9-Fluor-3-methyl-10-(4-ethyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazin-6-carbonsäure ist.

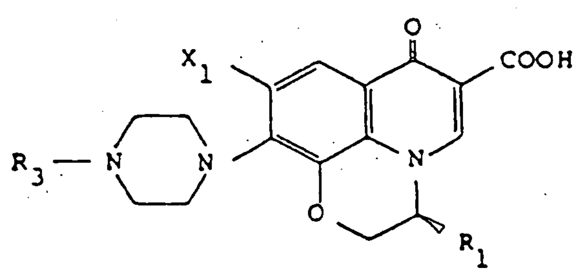
5. Verfahren zur Herstellung eines pharmazeutischen Mittels, wobei man mindestens eine Verbindung der Formel VI wie in den Ansprüchen 1 bis 4 definiert in einer zur Verabreichung geeigneten Form, gegebenenfalls zusammen mit einem üblichen Träger und/oder Diluens, zur Verfügung stellt.

6. Verwendung mindestens einer Verbindung der Formel VI wie in den Ansprüchen 1 bis 4 definiert zur Herstellung eines antimikrobiell wirksamen pharmazeutischen Mittels.

Revendications

Revendications pour les Etats contractants suivants : DE, GB, FR, IT, NL, SE, LI, CH, BE

1. Un dérive de S(-)-pyridobenzoxazine représente par la formule (VI)



(VI)

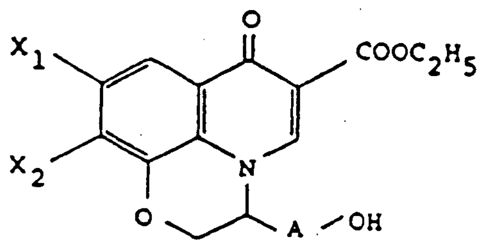
dans laquelle X_1 représente un atome de fluor, R_1 représente un groupe méthyle et R_3 représente un groupe méthyle ou un groupe éthyle.

2. L'acide S(-)-9-fluoro-3-méthyl-10-(4-méthyl-1-pipérazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]-benzoxazine-6-carboxylique selon la revendication 1.

3. L'acide S(-)-9-fluoro-3-méthyl-10-(4-éthyl-1-pipérazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]-benzoxazine-6-carboxylique selon la revendication 1.

4. Procédé pour la production des S-(-)-pyridobenzoxazines de formule (VI) selon les revendications 1-3, caractérisé en ce que

A) on traite un composé de formule générale (I')

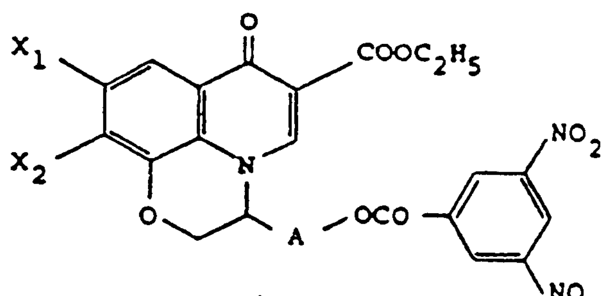


(±) (I')

dans laquelle X_1 a la signification donnée à la revendication 1, X_2 représente un atome d'halogène et

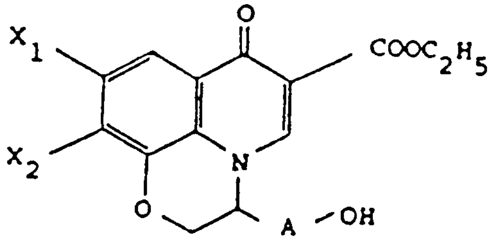
A représente un groupe méthylène,

avec le chlorure de 3,5-dinitrobenzoyle pour donner le (±)-3,5-dinitrobenzoate de formule générale (II')



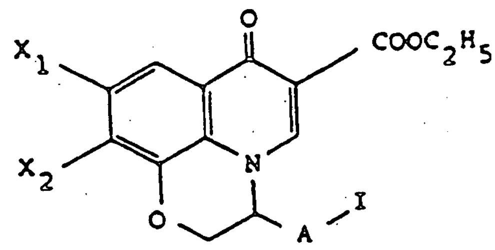
(II')

on résout optiquement le composé de formule générale (II') ainsi obtenu pour donner le composé S-(-) et on hydrolyse sélectivement le reste benzoate pour donner le composé hydroxyméthylène de formule générale (III')



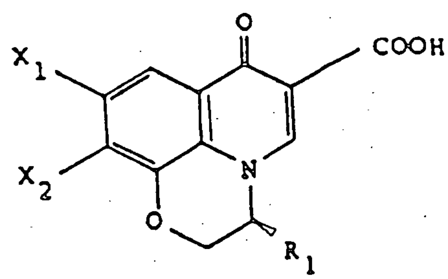
III'

on transforme le composé ainsi obtenu avec un réactif d'iodation pour donner le dérivé 3-iodométhylène de formule générale (IV')



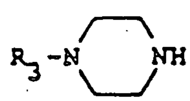
(IV')

on réduit le composé de formule générale (IV') ainsi obtenu pour donner le composé 3-méthylé et on l'hydrolyse en conditions acides pour donner l'acide 3-méthyl-6-carboxylique de formule générale (V)

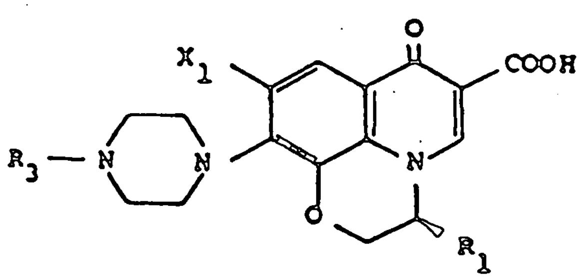


(V)

dans laquelle R_1 a les significations données à la revendication 1, et
on fait réagir le composé ainsi obtenu avec une N-alkyl-pipérazine de formule générale



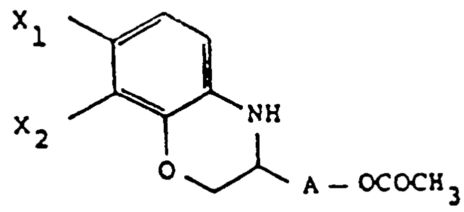
dans laquelle R_3 a les significations indiquées dans la revendication 1,
pour donner un composé de formule générale (VI)



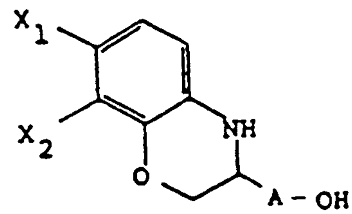
(VI)

ou bien
B) on fait réagir une 7,8-dihalogéno-2,3-dihydro-3-acétoxyméthylène-4H-[1,4]benzoxazine de formule générale (VII') avec une enzyme hydrolytique asymétrique pour récupérer un mélange comprenant le composé (VII') de départ riche en l'un ou l'autre des isomères optiques et un composé 3-

hydroxyméthylène (VIII')

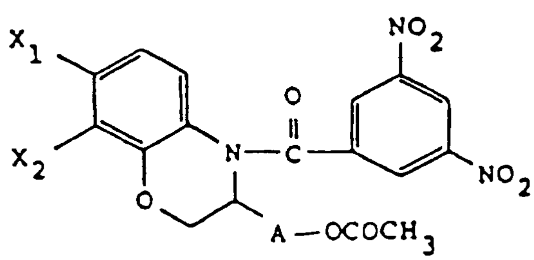


(VII')



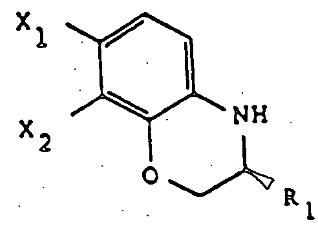
(VIII')

dans lesquelles A a les significations données ci-dessus,
on sépare le mélange en chaque composé,
on dinitrobenzoyle l'un ou l'autre de ces composés ou les deux et on acétyle ensuite le composé 3-hydroxyméthylène (VIII') benzoylé pour obtenir le composé de formule générale (IX')



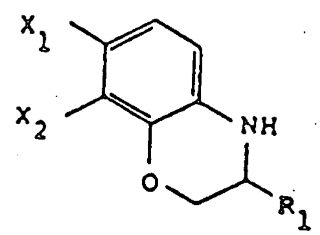
(IX')

on sépare le composé en les isomères optiques par cristallisation,
on soumet l'isomère 3-(-) résultant à la désacylation et la déshydroxylation par des procédés chimiques connus pour obtenir une 7,8-dihalogéno-2,3-dihydro-3-alkyl-4H-[1,4]benzoxazine (X) optiquement active



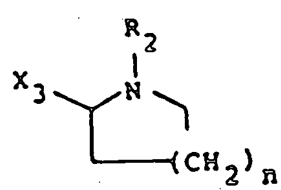
(X)

dans laquelle X_1, X_2 et R_1 ont les significations données ci-dessus, et
on obtient à partir de celle-ci comme décrit dans le procédé C un composé optiquement actif de formule générale (VI), ou bien
C) on condense un dérivé de 7,8-dihalogéno-1,4-benzoxazine de formule générale (X')



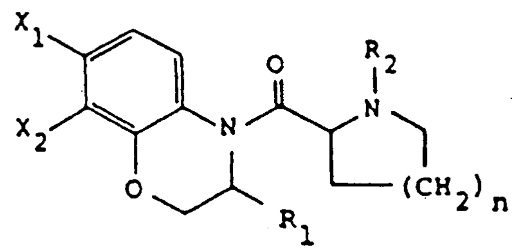
(X')

dans laquelle X_1, X_2 et R_1 ont les significations données ci-dessus,
avec un aminoacide cyclique ou un de ses dérivés réactifs de formule générale (XIV)



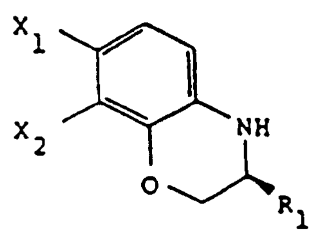
(XIV)

dans laquelle R_2 représente un groupe sulfonyle substitué, un groupe alcoxycarbonyle ou un groupe aralcoxycarbonyle,
n représente un entier de 1 à 3, et
X_3 représente un groupe carboxyle ou un de ses dérivés réactifs,
pour produire un composé de formule générale (X")



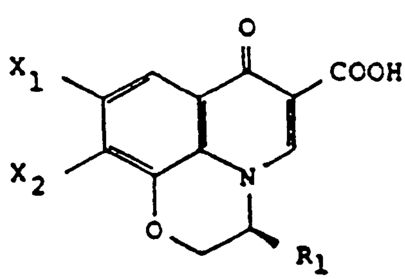
(X")

on sépare le mélange diastéréomère du composé de formule générale (X") obtenu et on hydrolyse le diastéréomère ainsi séparé pour donner une 7,8-dihalogéno-3-(S)-méthyl-[1,4]benzoxazine de formule générale (X)



(X)

on fait réagir le composé ainsi obtenu par des réactions connues pour donner un acide 9,10-dihalogéno-3-(S ou R)-méthyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]-benzoxazine-6-carboxylique de formule générale (V)

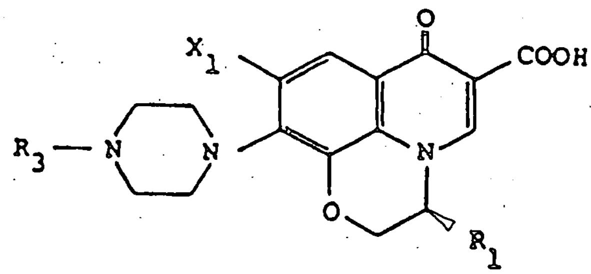


(V)

et

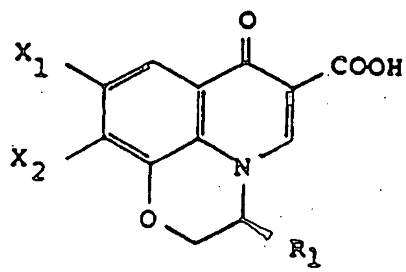
on transforme le composé ainsi obtenu comme décrit dans le procédé A) en un composé de formule générale (VI).

5. Un procédé pour préparer une S-(-)-pyridobenzoxazine représentée par la formule (VI)



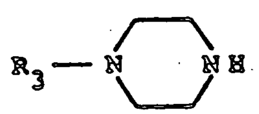
VI

dans laquelle X_1 représente un atome de fluor, R_1 représente un groupe méthyle et R_3 représente un groupe méthyle ou ou un groupe éthyle, qui consiste à faire réagir un dérivé de S-(-)-9-fluoro-10-halogéno-pyridobenzoxazine représenté par la formule (V) ou son produit de réaction avec le trifluorure de bore,



V

dans laquelle X_1 et R_1 ont les significations données ci-dessus et X_2 représente un atome d'halogène, avec une N-alkyl-pipérazine représentée par la formule suivante



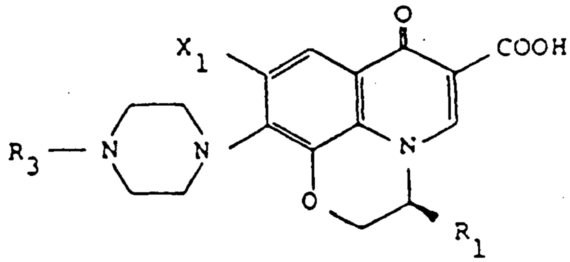
dans laquelle R_3 a les significations données ci-dessus.

6. Composition pharmaceutique contenant au moins un composé selon les revendications 1 à 3, facultativement en combinaison avec un support et/ou un diluant habituels.

7. L'utilisation d'au moins un composé selon l'une quelconque des revendications 1 à 3, pour préparer une composition pharmaceutique douée d'activité antimicrobienne.

Revendications pour l'Etat contractant suivant : AT

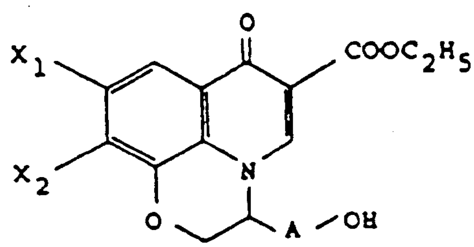
1. Un procédé pour produire un dérivé de S(-)-pyridobenzoxazine représenté par la formule (VI)



(VI)

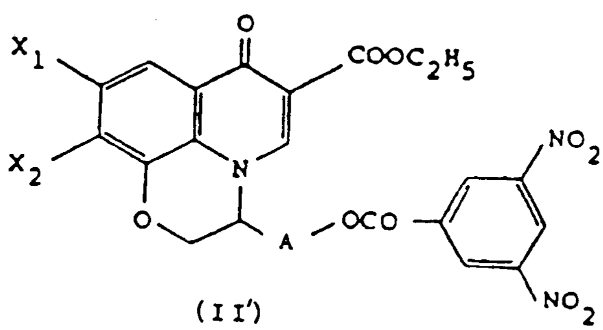
dans laquelle X_1 représente un atome de fluor, R_1 représente un groupe méthyle et R_3 représente un groupe méthyle ou un groupe éthyle
caractérisé en ce que

A) on traite un composé de formule générale (I')



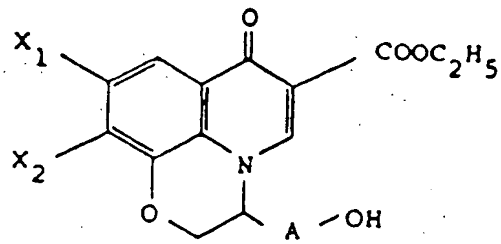
(±) (I')

dans laquelle X_1 a la signification donnée ci-dessus, X_2 représente un atome d'halogène et A représente un groupe méthylène,
avec le chlorure de 3,5-dinitrobenzoyle pour donner le (±)-3,5-dinitrobenzoate de formule générale (II')



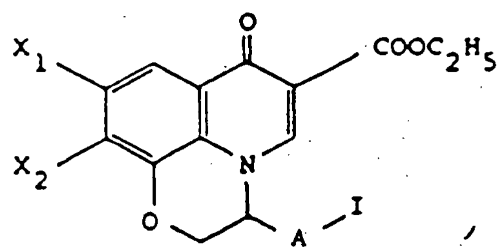
(II')

on résout optiquement le composé de formule générale (II') ainsi obtenu pour donner le composé S-(-) et on hydrolyse sélectivement le reste benzoate pour donner le composé hydroxyméthylène de formule générale (III')



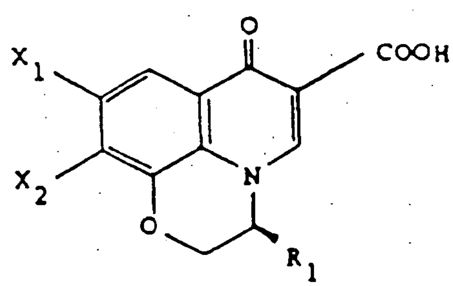
III'

on transforme le composé ainsi obtenu avec un reactif d'iodation pour donner le dérivé 3-iodométhylène de formule générale (IV')



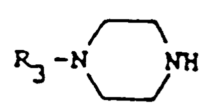
(IV')

on réduit le composé de formule générale (IV') ainsi obtenu pour donner le composé 3-méthylé et on l'hydrolyse en conditions acides pour donner l'acide 3-méthyl-6-carboxylique de formule générale (V)

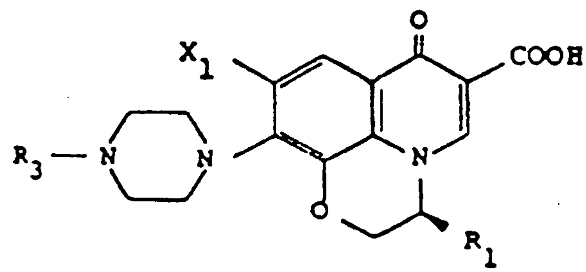


(V)

dans laquelle R_1 a les significations données ci-dessus, et
on fait réagir le composé ainsi obtenu avec une N-alkyl-pipérazine de formule générale



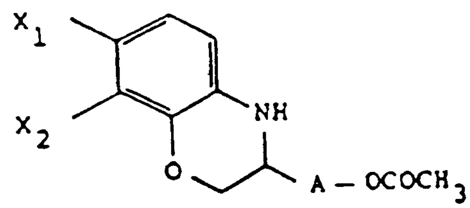
dans laquelle R_3 a les significations indiquées ci-dessus,
pour donner un composé de formule générale (VI)



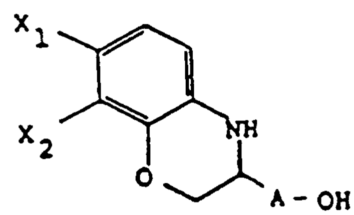
(VI)

ou bien

B) on fait réagir une 7,8-dihalogéno-2,3-dihydro-3-acétoxyméthylène-4H-[1,4]benzoxazine de formule générale (VII') avec une enzyme hydrolytique asymétrique pour récupérer un mélange comprenant le composé (VII') de départ riche en l'un ou l'autre des isomères optiques et un composé 3-hydroxyméthylène (VIII')



(VII')

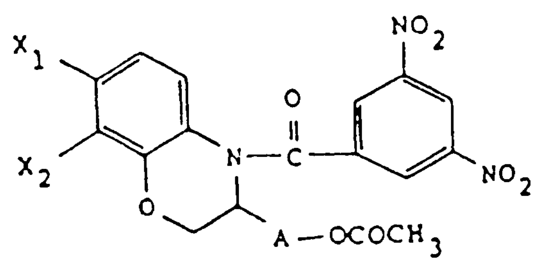


(VIII')

dans lesquelles A a les significations données ci-dessus,

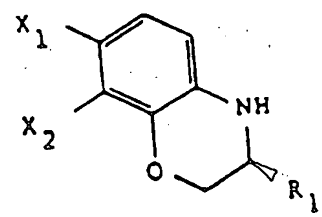
on sépare le mélange en chaque composé,

on dinitrobenzoyle l'un ou l'autre de ces composés ou les deux et on acétyle ensuite le composé 3-hydroxyméthylène (VIII') benzoylé pour obtenir le composé de formule générale (IX')



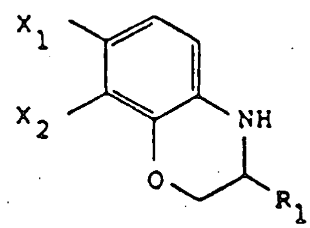
(IX')

on sépare le composé en les isomères optiques par cristallisation,
on soumet l'isomère 3-(-) résultant à la désacylation et la déshydroxylation par des procédés chimiques connus pour obtenir une 7,8-dihalogéno-2,3-dihydro-3-alkyl-4H-[1,4]benzoxazine (X) optiquement active



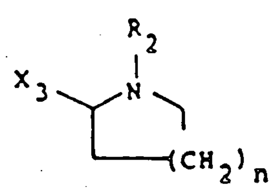
(X)

dans laquelle X_1, X_2 et X_3 ont les significations données ci-dessus, et
on obtient à partir de celle-ci comme décrit dans le procédé C un composé optiquement actif de formule générale (VI), ou bien
C) on condense les dérivés de 7,8-dihalogéno-1,4-benzoxazine de formule générale (X')



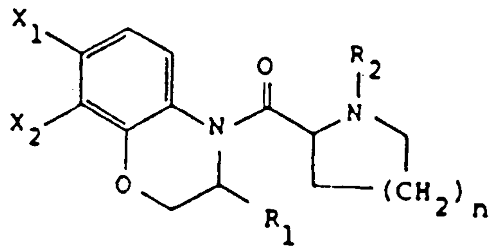
(X')

dans laquelle X_1, X_2 et R_1 ont les significations données ci-dessus,
avec un aminoacide cyclique ou un de ses dérivés réactifs de formule générale (XIV)



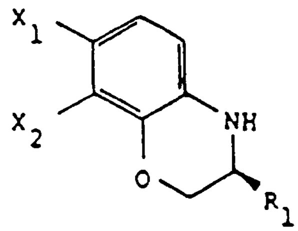
(XIV)

dans laquelle R_2 représente un groupe sulfonyle substitué, un groupe alcoxycarbonyle ou un groupe aralcoxycarbonyle,
n représente un entier de 1 à 3, et
X_3 représente un groupe carboxyle ou un de ses dérivés réactifs,
pour produire un composé de formule générale (X")



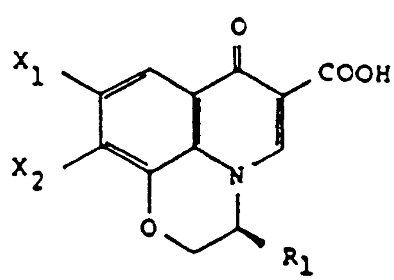
(X")

on sépare le mélange diastéréomère du composé de formule générale (X") obtenu et on hydrolyse le diastéréomère ainsi séparé pour donner une 7,8-dihalogéno-3-(S)-méthyl-[1,4]benzoxazine de formule générale (X)



(X)

on fait réagir le composé ainsi obtenu par des réactions connues pour donner un acide 9,10-dihalogéno-3-(S ou R)-méthyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylique de formule générale (V)

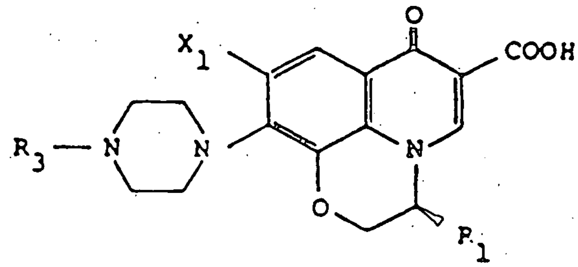


(V)

et

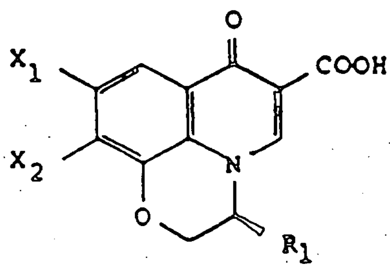
on transforme le composé ainsi obtenu comme décrit dans le procédé A) en un composé de formule générale (VI).

2. Un procédé pour préparer un dérivé de S(-)pyridobenzoxazine représenté par la formule (VI)



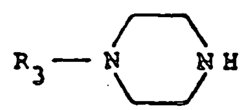
VI

dans laquelle X_1 représente un atome de fluor, R_1 représente un groupe méthyle et R_3 représente un groupe méthyle ou un groupe éthyle, qui consiste à faire réagir un dérivé de S-(-)-9-fluoro-10-halogéno-pyridobenzoxazine représenté par la formule (V) ou son produit de réaction avec le trifluorure de bore,



V

dans laquelle X_1 et R_1 ont les significations données ci-dessus et X_2 représente un atome d'halogène, avec une N-alkyl-pipérazine représentée par la formule suivante



dans laquelle R_3 a les significations données ci-dessus.

3. Le procédé selon la revendication 1 ou 2, dans lequel le composé obtenu est l'acide S(-)-9-fluoro-3-méthyl-10-(4-méthyl-1-pipérazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylique.

4. Le procédé selon la revendication 1 ou 2, dans lequel le composé obtenu est l'acide S(-)-9-fluoro-3-méthyl-10-(4-éthyl-1-pipérazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylique.

5. Un procédé pour préparer une composition pharmaceutique qui consiste à former au moins un composé de formule (VI) tel que défini dans les revendications 1 à 4 sous une forme appropriée pour l'administration, facultativement incorporé dans un support et/ou un diluant habituels.

6. L'utilisation d'au moins un composé de formule (VI) tel que défini dans les revendications 1 à 4 pour préparer une composition pharmaceutique douée d'activité antibactérienne.